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BRONCHIOGENIC CARCINOMA

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THIS report has a two-fold purpose: first, to emphasize the value of aspiration biopsy in the practical diagnosis of cancer of the lung, and, second, to emphasize the value of roentgen irradiation in the treatment of that disease.

Based on a review (Table IA) of 401 cases in the files for cancer of the lung at the Memorial Hospital, from 1918 to July 1, 1939, the report is restricted to 175 cases that have been regarded as having satisfactory histologic proof of the diagnosis during the years 1920 to July 1, 1939. It is probable that a high proportion of the cases that were not analyzed, 226 in number, were also cases of cancer of the lung, but in them there was either no histological material available, or the pathologic diagnosis was so questionable that they were excluded. In addition, there were a few cases in which the evidence strongly suggested that the lung tumor was secondary to a primary carcinoma of some other organ.

Age and Sex Incidence. The average age on admission was 53.8 years. By subtracting the elapsed time from apparent onset to admission, the figure for the average age at onset becomes exactly fifty-three years (see Table IB).

The great preponderance of the male sex found in nearly all studies of lung cancer is strikingly emphasized in this series

TABLE IA

CARCINOMA OF LUNG FILE
MEMORIAL HOSPITAL

Year	Proved	Unproved	Total
1918	0	4	4
1919	0	8	8
1920	1	5	6
1921	1	9	10
1922	0	16	16
1923	1	6	7
1924	3	5	8
1925	1	14	15
1926	1	13	14
1927	2	9	11
1928	3	17	20
1929	2	9	11
1930	8	9	17
1931	10	15	25
1932	9	21	30
1933	18	14	32
1934	20	14	34
1935	21	13	34
1936	20	9	29
1937	21	3	24
1938	24	9	33
1939	9	4	13
Totals	175	226	401

Note that below the line, that is after 1932, the number of proved cases exceeds the number of unproved cases in each year.

TABLE IB

BRONCHIOGENIC CARCINOMA

Age (average) on admission	53.8
Age (average) at onset	53.0

* From the Memorial Hospital, New York. Read at the International Cancer Congress, Atlantic City, N. J., September, 1939.

(see Table II). For the whole group, the sex incidence was 90.3 per cent in men, 9.7 per cent in women. It was noticed that in the earlier years of the twenty year period covered by the 175 proved cases, this disproportion between men and women was less marked. Therefore, the sex incidence

TABLE II

BRONCHIOGENIC CARCINOMA; SEX INCIDENCE IN 175 CASES

	Men	Women
Whole group	90.3%	9.7%
1920 to 1929	73.3	26.7 (15 cases)
1930 to 1939	91.9	8.1 (160 cases)
First half of group	85.1	14.9 (87 cases to May, 1935)
Second half of group	95.5	4.5 (88 cases May, 1935 to July 1, 1939)

was re-analyzed in two ways. For the first ten years, 1920 to 1929, inclusive, the sex incidence was 73.3 per cent men, 26.7 per cent women; while for the second ten years, 1930 to 1939 inclusive, the sex incidence was 91.9 per cent in men, 8.1 per cent in women. Inasmuch as these percentages are based on only 15 cases for the first ten year period, it seemed advisable to compare the sex incidence in the first half of the 175 cases with that for the second half. Here again we find that there seems to be an increase in the greater incidence in the male sex in recent years. Taking the first 87 cases, running from 1920 to May, 1935, the sex incidence is 85.1 per cent in males, 14.9 per cent in females; while in the second half, comprising 88 cases from May, 1935, to July 1, 1939, the sex incidence is 95.5 per cent in males, 4.5 per cent in females.

The significance for the epidemiology of cancer of the lung in these figures, which seem to indicate a changing sex incidence, giving even greater liability to males in recent years, should not be judged until there has been a study of a much larger series from various sources, as our figures may merely represent an unusual set of circumstances.

THE DIAGNOSIS OF BRONCHIOGENIC CARCINOMA

Final Proof. The methods by which final proof of the diagnosis was considered to have been made in this series of 175 cases are tabulated in Table III. The methods are arranged in order, according to the likely degree of certainty of proof, beginning with autopsy. Autopsy was done in 34 cases, or 19.4 per cent of the whole group. Tissue removed from a lung tumor at thoracotomy, or an expectorated macroscopic piece of tissue accounted for 10

TABLE III

BRONCHIOGENIC CARCINOMA—175 CASES METHOD OF FINAL PROOF OF DIAGNOSIS

Method	Total by the Method	Alone by the Method	Supplemented by Autopsy	Supplemented by Other Methods
Autopsy	34	15	—	19
Thoracotomy	8	7	1	0
Expectorated tissue	2	0	1	1
Bronchoscopy	80	59	11	10
Aspiration of lung	66	58	2	6
Aspiration of rib	1	1	0	0
Aspiration of lymph node	1	1	0	0

cases. In 2 of these cases, the diagnosis was confirmed by autopsy. In 7 cases, or 4.0 per cent, the diagnosis rests alone on tissue removed by thoracotomy.

As for bronchoscopy, the diagnosis rests alone on tissue removed by this means in 59 cases, or 33.7 per cent. In 11 other cases the proof by tissue removed at bronchoscopy was confirmed by autopsy, and in 10 further cases, there was additional histological proof by other means, such as examination of excised nodes involved by metastases or of material aspirated from metastatic tumors in lymph nodes or bone.

As for aspiration biopsy of the lung tumor, it will be noted in Table III that a

considerable proportion of the cases in this series, namely 58 cases, or 33.1 per cent, has been accepted as proved cases of primary bronchiogenic carcinoma on the sole basis, as far as tissue examination is concerned, of specimens removed from the lung by this method.

To critics of the inclusion of 33 per cent of the cases in this series on the basis of tissue removed from the lung by aspiration biopsy, the following statements are made:

It is frankly admitted that in general the bits of tissue removed through a bronchoscope lend themselves somewhat more readily to the skilled pathologist's interpretation of type and grading of carcinoma than do the smears made of material obtained by aspiration biopsy. However, a careful sectioning of the small clots and fragments of tissue obtained with the aspirating needle may yield sections every bit as good and sometimes better than crushed scrapings obtained with a bronchoscope.

The method of aspiration biopsy requires considerable technical experience and cooperation all the way through, including the roentgenological localization of the tumor, the technique of the aspiration, the meticulous saving of every bit of tissue obtained, the careful technique of preparation of slides, and finally the skill of the pathologist in finding significant bits of tissue and in interpreting them.

When on such a basis a diagnosis of carcinoma is made, frequently even as to whether it is epidermoid or adenocarcinoma, and a clinical survey of the patient yields no sign of primary carcinoma elsewhere, one may feel justified in assuming that the case is one of primary lung carcinoma. After all, bronchoscopic removal of carcinoma does by no means make certain that the tumor is primary in the lung, since it is quite possible for metastatic tumors to erode the bronchial wall. The same criteria in judging whether a carcinoma is primary in the lung must be applied in a large measure to cases with bronchoscopic biopsies as to those with aspiration biopsies.

In our series of aspiration biopsies, in addition to the 58 cases in which this method was the only proof, there were 2 cases in which autopsy confirmed the diagnosis and 6 cases in which the proof was supplemented histologically from other sources, such as excised metastatic lymph nodes, aspiration of nodes, aspiration of metastatic lesions in bone, and tissue removed bronchoscopically (2 cases).

In one case the histologic diagnosis rests alone upon aspiration of a rib. Since this was a case in which the lung tumor was contiguous to and had directly invaded the rib, it may be considered practically the same as an aspiration of the lung.

In one case the proof histologically rests on an aspiration of a lymph node. With this one exception, all cases in which proof would have to depend on *either aspiration or excision* of a lymph node have been excluded. This case was included because the tumor was a bulky left apical carcinoma destroying portions of the left first and second ribs and lying very close to the involved left supraclavicular lymph node from which the specimen was aspirated.

As far as proof of primary lung origin is concerned, it may be stated that no case can be looked upon with absolute certainty unless an autopsy unqualifiedly demonstrates both grossly and microscopically in the opinion of an experienced tumor pathologist that the the primary site is in the lung. Some autopsied cases have had to be excluded from this report because a review of their material this year showed that they were primary carcinomas of other than bronchial origin.

Proof of Diagnosis for Purpose of Treatment. In Table IV are summarized the methods by which the diagnosis was made in preparation for treatment. Bronchoscopy (80 cases, 45.7 per cent) and aspiration biopsy (64 cases, or 36.5 per cent) are the chief means used in this series to obtain tissue proving that the patient has a carcinoma of the lung before a decision is made about the method of treatment.

It is important to know, if possible, that

a patient has carcinoma of the lung before deciding that he is to be subjected to treatment for that disease since the treatment is severe. The thoracotomies (8 cases, 4.6 per cent) listed in this table were, with one exception, done elsewhere before the patient was referred to Memorial Hospital. As a purely diagnostic procedure, thoracotomy is a rather severe procedure to impose on a patient suspected of having bronchial carcinoma. By contrast, bronchoscopy and particularly aspiration biopsy are brief, less hazardous and cause much less delay in subsequent procedures.

TABLE IV

BRONCHIOGENIC CARCINOMA; METHOD OF DIAGNOSIS FOR TREATMENT IN 175 CASES

Bronchoscopy	80
Thoracotomy	8
Expectorated tissue (confirmation by this means in 2 cases)	0
Aspiration biopsy of lung	64
Lymph nodes excised or aspirated (confirmation by this means in 5 cases)	7
Aspiration of rib (directly invaded from lung)	1
No tissue during life (all confirmed by autopsy)	15
Total	175

The examination of tissue from an accessible swollen lymph node, the seat of metastatic carcinoma, may be of help in proving that the patient has carcinoma arising somewhere within the drainage field of that node, but it is often difficult for the pathologist to determine whether the structure is consistent with origin from lung. The examination of sedimented or centrifuged pleural exudates is notoriously unreliable. Therefore, it is better to avoid if possible relying entirely on evidence from lymph nodes or pleural fluids in making a diagnosis of carcinoma of the lung.

Bronchoscopic Examination. Removal of a biopsy bronchoscopically is preferred to aspiration biopsy in all cases in which it seems at all feasible to have a bronchoscopic examination done. If an actual bit of tissue can be secured through the bronchoscope it is likely to show cellular arrangement and thus to permit a diagnosis of type, grade, and radiosensitivity of the tumor more readily than the usual aspiration biopsy. The aspiration biopsy may permit only a diagnosis of malignant tumor, more commonly a diagnosis of carcinoma, less frequently a diagnosis of type, such as epidermoid carcinoma, and seldom much information as to grade and radiosensitivity. However, the careful sectioning of the small clot or of gross tissue fragments obtained by aspiration biopsy may yield excellent sections, indistinguishable in some cases from regular sections from routine gross material.

Experience at Memorial Hospital may be somewhat exceptional, in that perhaps some unusually difficult cases for diagnosis have been referred there. Certainly the experience there does not bear out the assertion that bronchial carcinoma can be diagnosed early and with certainty in a very high proportion of cases. As will be seen from Table IV, were it not for aspiration biopsy 64 cases, or 36.5 per cent, of this series would not have been diagnosed, since the use of this method implies that bronchoscopy had failed to obtain proof, or that bronchoscopy was obviously not applicable. The contrast between waiting to have a thoracotomy, or waiting for a tumor to grow along a bronchus so that it becomes accessible, on the one hand, and on the other hand, the obtaining of a diagnosis of carcinoma within thirty minutes by aspiration biopsy, is very impressive to those who have had an opportunity to witness the two experiences.

In 26 cases in which bronchoscopy was done and was negative or had failed to obtain carcinoma (once in 22 cases, twice in 2 cases, three times in 1 case, and four times in 1 case) aspiration was done and obtained the diagnosis.

A reflection of the necessity of relying on aspiration biopsy in order to prove the diagnosis before treatment in many cases in which such diagnosis was not afforded by bronchoscopy or thoracotomy is shown in Table V. Beginning in 1927 and with increased frequency since 1934, it has been found necessary to resort to aspiration.

As one reason for this, a review of the

anatomical locations of the tumors in the lung reveals that a considerable proportion of them lie far out. However, several that were situated close to the mediastinum proved to have no tissue accessible to the bronchoscope. There is a considerable group of bulky mediastinal or juxtahilar carcinomas of the lung which apparently arise not from the main bronchi, but from medially situated minor branch bronchi. They may show some compression, fixation, or distortion of the major bronchi, but no accessible material for bronchoscopic biopsy.

Table V

COMPARISON OF LEADING METHODS OF DIAGNOSIS FOR TREATMENT OF BRONCHIOGENIC CARCINOMA BY YEARS

	Bronchoscopy	Thoracotomy	Aspiration
1920	1	0	0
1921	0	1	0
1922	0	0	0
1923	0	1	0
1924	1	1	0
1925	0	1	0
1926	1	0	0
1927	1	0	1
1928	1	1	1
1929	2	0	0
1930	4	0	1
1931	6	0	3
1932	5	0	3
1933	11	0	3
1934	12	2	3
1935	10	0	9
1936	8	0	10
1937	4	0	15
1938	9	0	13
1939	4	1	2

In 15 cases in which no histologic proof of diagnosis was obtained during life and in which therefore treatment when given was given with considerable uncertainty, the diagnosis was confirmed by autopsy in all.

The Histologic Types (See Table VI). It was not possible to fit all cases into the commonly accepted three categories of epidermoid carcinoma, adenocarcinoma, and anaplastic carcinoma. Two additional groups had to be made: (1) bronchiogenic carcinoma, in which the growth is undoubtedly of bronchial origin, but it is impossible to classify it as epidermoid carcinoma or adenocarcinoma; and (2) "carcinoma"—a diagnosis often the best that can be made from the bits of tissue obtained by bronchoscopy or aspiration biopsy. Table VI shows that the squamous and epidermoid group accounts for nearly half the cases, bronchiogenic, adenocarcinoma, and anaplastic each for about one-tenth, and the unclassified "carcinoma" for about one-fifth.

Table VI

BRONCHIOGENIC CARCINOMA HISTOLOGIC TYPES IN 175 CASES

	No.	Per cent
Squamous and epidermoid carcinoma	85	49
Bronchiogenic carcinoma	16	9
Adenocarcinoma	18	10
Anaplastic carcinoma	19	11
"Carcinoma"	37	21
Total	175	100

Treatment of Bronchiogenic Carcinoma by Irradiation. The study of results of treatment in these 175 cases is based on a follow-up which shows 20 patients living, 140 dead of the disease, and 15 untraced (Table VII).

Table VII

BRONCHIOGENIC CARCINOMA FOLLOW-UP OF 175 CASES

Living	20
Died of the disease	140
Lost to follow-up	15
Total	175

The methods of treatment used in this series are shown in Table VIII. Two patients referred to Dr. George Heuer and operated on by him and his associates at New York Hospital after the diagnosis had been established at Memorial Hospital (in one by aspiration and in one by bronchoscopic biopsy) are included. Seventeen were not treated. One hundred and forty-two were treated with roentgen rays (200 to 700 kv.) and 14 were treated by the radon or radium element pack.

TABLE VIII

BRONCHIOGENIC CARCINOMA
METHODS OF TREATMENT IN 175 CASES

Roentgen therapy	142
Radium pack	14
Operation (elsewhere)	2
Untreated	17
Total	175

Duration of Life in Untreated Cases (See Table IX). Of the 17 untreated cases, 3 were untraced and in one the data are incomplete. In the remaining 13 cases, the total duration of the disease, from the time of apparent onset until death, averaged 14.8 months, and varied from 2.2 to thirty-nine months. Four of these untreated patients survived over two years, assuming that the estimate of the time of onset is correct. It does not seem advisable to try to make a comparison between the duration after admission of these untreated patients with the duration after admission of treated patients, since the fact that they were not treated would in general mean that they came considerably later in their course than did the treated patients. However, for the sake of completeness the duration of life in the untreated patients after admission is included here. It averaged 2.4 months, varying from five hours to 11.4 months.

TABLE IX

BRONCHIOGENIC CARCINOMA

Untreated Cases	Follow-up
Living	0
Died	14
Lost	3
Total	17

In 13 of those who died, the total duration, from time of apparent onset to death varied from 2.2 to 39 months (4 over 2 years), and averaged 14.8 months.

Method of Estimating Value of Irradiation. As a means of attempting to estimate the value of irradiation in palliation of symptoms, the records of all the deceased irradiated patients have been studied and the degree of clinical palliation has been graded on a scale of 0, 1, 2, and 3 (in which 0 represents no improvement and 3 represents very marked palliation). Judgment of degree of palliation was made as objectively as possible based on records reporting such factors as gain of weight, lessening or disappearance of cough, hemoptysis, pain, and wheezing, and restoration of the patient's ability to work. At the same time, the duration of life in months following treatment has been recorded.

The cases have been classified by histologic type and by the dose in roentgens estimated to have been delivered to the tumor. In the cases treated by the radon or radium pack, the dose estimated in roentgens must of course be taken with some reservation as to whether it is at present entirely justifiable to compare radium roentgens with x-ray roentgens.

It must further be stated that in these tables (except Table XIB) the dose refers only to that delivered in the initial cycle. Many of the patients in the roentgen-treated group had subsequent cycles of irradiation which gave them a much greater total tumor dose than is shown here. These cycles followed at intervals of 1.5 to many months. If one took into account all the radiation delivered to the tumor, one could make out what would seem at first glance to be a strong case for a statement that patients receiving the larger total doses showed much better palliation and survived considerably longer on the average (see Table XIB). However, this would be open to at least two objections: (1) those who were in better condition to start with naturally lived longer and could receive more cycles of treatment and therefore a heavier total dose; (2) it is not usually considered proper to add together doses delivered at intervals of several months in computing tumor doses. Of course, the first objection is valid to some extent, even if the dose in only the initial cycle is used, since those in better condition at the beginning are also likely to be able to stand a larger initial cycle. However, the objection seems somewhat weaker in this case, and in the face of the difficult problem

TABLE X

BRONCHIOGENIC CARCINOMA

RESULTS IN CASES TREATED BY RADIUM PACK IN RELATION TO TUMOR DOSE IN ROENTGENS AND HISTOLOGIC TYPE

Type	0–1000 r				1000–2000 r			
	Cases	Palliation 0–1–2–3	Before	After	Cases	Palliation 0–1–2–3	Before	After
Squamous and epidermoid	3	2–1–0–0	6.6	3.4	1	1–0–0–0	13.0	1.0
Bronchiogenic	3	2–1–0–0	4.7	3.7	1	1–0–0–0	12.5	2.5
Adenocarcinoma	3	2–1–0–0	3.7	2.3	0	—	—	—
Anaplastic	1	1–0–0–0	4.3	2.5	0	—	—	—
Total	10	7–3–0–0	4.9	3.1	2	2–0–0–0	12.8	1.8
			Av.				Av.	

of trying to gain some proper estimate of the palliative effects of irradiation, it seemed better to reduce the analysis to terms of the roentgens in the initial cycle only, as indicating the degree of thoroughness of the first course of treatment.

The duration of symptoms before treatment is included to try to meet the objection that cases with longer durations after treatment may have been ones with naturally slower courses. However, this point might be argued two ways: on the one hand, if a longer pre-treatment average is found for those patients living longer after treatment, the objection that they were naturally of slower course could be raised. On the other hand, if a shorter pre-treatment duration is found for those living longer after treatment, it could be argued that on the average, they had applied for treatment earlier in their course and therefore might be expected to survive longer, whether irradiated or not.

Cases Treated by Radium. Inspection of Table x, showing the cases treated by the radon or radium element pack (at distances from 6 to 20 cm.), reveals that in the 10 cases treated that are suitable for analysis, the results were not at all good. In the light of more recent experience with irradiation, it seems likely that the large radium doses entailed too much irradiation of large sections of the body, in proportion to what could be delivered to the tumor.

Cases Treated by Roentgen Rays. Table XIA shows that as the tumor dose in roentgens is increased in the initial cycle, the duration of life following treatments increases. Cases receiving from 2,000 to 3,000 r in the tumor survived an average of 8.2

TABLE XIA

BRONCHIOGENIC CARCINOMA

RESULTS VS. HISTOLOGIC TYPES AND ROENTGENS TO TUMOR IN INITIAL CYCLE IN CASES TREATED BY ROENTGEN RAYS

Histologic Type	0–1000 r				1000–2000 r				2000–3000 r				3000–4000 r			
	No.	Palliation 0–1–2–3	Before	After	No.	Palliation 0– 1–2–3	Before	After	No.	Palliation 0– 1– 2–3	Before	After	No.	Palliation 0–1–2–3	Before	After
Squamous and epidermoid	14	11–2–0–1	12.2	5.1	21	8– 8–5–0	12.0	6.4	22	4–10– 7–1	8.6	8.6	2	0–2–0–0	4.5	7.0
Bronchiogenic	2	0–2–0–0	7.1	5.1	2	2– 0–0–0	4.5	2.6	4	2– 0– 2–0	15.1	7.9	0	—	—	—
Adenocarcinoma	1	1–0–0–0	6.5	0.3	4	3– 1–0–0	12.8	6.3	4	3– 0– 1–0	24.2	7.4	1	0–1–0–0	3.8	3.8
Anaplastic "Carcinoma"	4	4–0–0–0	11.9	2.4	6	3– 1–1–1	12.4	5.3	4	0– 3– 1–0	2.3	6.3	0	—	—	—
	7	5–2–0–0	4.6	4.2	7	2– 2–3–0	11.2	7.4	5	0– 2– 3–0	11.9	9.0	1	1–0–0–0	5.0	3.8
	28	21–6–0–1	9.9	4.3	40	18–12–9–1	11.6	6.2	39	9–15–14–1	10.7	8.2	4	1–3–0–0	4.4	5.4
			Av.				Av.				Av.				Av.	

TABLE XIB

RESULTS IN ROENTGEN IRRADIATED PATIENTS NOW DECEASED CONSIDERING TOTAL TUMOR DOSE IN ALL CYCLES VS. TUMOR DOSE IN INITIAL CYCLE ONLY

Tumor Dose		No. of Cases	Palliation 0- 1- 2-3	Months' Duration		
				Before	After	Total
Under 1000 r	All cycles	22	19- 3- 0-0	10.1	3.5	13.6
	Initial cycle	28	21- 6- 0-1	9.9	4.3	14.2
1000–2000 r	All cycles	32	17-11- 3-1	12.4	4.4	16.8
	Initial cycle	40	18-12- 9-1	11.6	6.2	17.8
2000–3000 r	All cycles	29	10-14- 4-1	8.7	6.2	14.9
	Initial cycle	39	9-15-14-1	10.7	8.2	18.9
3000–4000 r	All cycles	28	3- 8-16-1	11.0	11.1	22.1
	Initial cycle	4	1- 3- 0-0	4.4	5.4	9.8
				Bef. adm.	Aft. adm.	Total
(Untreated)		13	—	12.4	2.4	14.8

months, as compared with an average survival of only 4.3 months in those receiving less than 1,000 r in the tumor. These figures may be compared with the average survival after admission of 2.4 months in the untreated cases. In the 3,000 to 4,000 r group, as there are only 4 cases (keeping in mind that this represents the initial cycle only) the number seems too few to put any significance on the drop in survival to 5.4 months. Considering either total doses or doses in the first cycles only, there is a marked trend toward improved palliation as the tumor dose increases (Tables XIA and XIB).

As between the various histological types of carcinoma, there seems to be hardly a significant difference in the survival figures, but the grades of palliation seem to favor the epidermoid group as against adenocarcinoma and anaplastic carcinoma.

Results in Living Patients. Of the 20 living patients, one is one of the patients operated on ten months ago by Dr. George Heuer. Although only a right middle and lower lobectomy was done, this patient

TABLE XII

BRONCHIOGENIC CARCINOMA

LIVING PATIENTS: RESULTS VS. TYPE AND TUMOR DOSE IN ROENTGENS (IN INITIAL CYCLE)

	1000–2000 r				2000–3000 r				3000–4000 r			
	Cases	Palliation 0-1-2-3	Before	After	Cases	Palliation 0-1-2-3	Before	After	Cases	Palliation 0-1-2-3	Before	After
Squamous and epidermoid	1	0-0-0-1	30.0	149.9	6	0-3-1-2	11.8	20.1	1	1-0-0-0	13.0	5.7
Bronchiogenic	—	—	—	—	2	0-2-0-0	5.7	2.1	—	—	—	—
Adenocarcinoma	—	—	—	—	—	—	—	—	1	0-1-0-0	9.8	5.7
Anaplastic	—	—	—	—	—	—	—	—	—	—	—	—
"Carcinoma"	1	0-1-0-0	2.5	6.9	4	0-1-1-2	12.6	26.8	1	0-0-1-0	8.0	4.7
Total	2	0-1-0-1	?	?	12	0-3-1-2	11.1	19.3	3	1-1-1-0	10.3	5.4
							Av.				Av.	

has gained 60 pounds and seemed free of disease when last seen one month ago. Two of the living patients are of too recent accession to be suitable for analysis. Table XII shows for the remaining 17 living patients, all of whom were treated by roentgen rays, the data concerning tumor dose in the initial cycle, palliation, and duration in months before and after treatment, just as is shown for the deceased irradiated cases. The shorter duration in some groups of the living patients of course means nothing as yet.

Five, Four, Three and Two Year Survival Rates (See Table XIII). The five year survival rates are discouragingly low. Based on all proved cases regardless of whether treated or untreated, followed or lost, it is only 2.8 per cent. Based on cases treated by roentgen rays it is 3.8 per cent. Even the two year survival rate in cases treated by roentgen rays, the more favorable of the two irradiated groups, is only a little under 7 per cent.

Therefore, we still have to point largely toward palliative effect and possible prolongation of life in an almost uniformly fatal disease in speaking of the value of irradiation in carcinoma of the lung.

These palliative effects are certainly very striking in certain individual instances.

Discussion of Irradiation of Carcinoma of Lung. The evidence here presented suggests that roentgen irradiation is more effective than external irradiation by radium in the treatment of carcinoma of the lung. The figures for palliative results and survival after treatment in the deceased patients indicate the probability of improved results in proportion to the approach to a cancericidal dose delivered to the tumor. It is obvious that, considering even the total dose delivered in repeated cycles over periods of many months, a cancericidal dose has not as a rule been delivered. It may be that there is a threshold limit of tolerance of lung tissue to irradiation beyond which one cannot go without producing undesirable and deleterious effects which might for practical purposes negate the benefits of a control of the cancer process in the lung. It is the studied opinion of the writer, however, that very few indications of such a limitation of tolerance of lung tissue have been seen in this series, and that it is going to be possible, within the next few years, to deliver safely considerably more radiation to lung carcinomas than has been done in the past. A well chosen plan for cross-

TABLE XIII

BRONCHIOGENIC CARCINOMA
FIVE YEAR, FOUR YEAR, THREE YEAR, AND TWO YEAR SURVIVALS AS OF JULY, 1939.

(All patients surviving over 2 years were treated by roentgen rays)

	All Cases	Roentgen Rays and Radium	Roentgen Rays Alone*
	per cent	per cent	per cent
Survived over five years	2.8	3.1	3.8
Survived over four years	3.3	3.7	4.4
Survived over three years	3.6	4.1	4.8
Survived over two years	5.4	6.1	6.9

* One patient in this group had a few radium pack treatments.

firing, longer target-skin distances, higher voltages, and greater filtration are the technical factors that will permit increased tumor dosage.

In recent years at Memorial Hospital, the efforts in treating lung carcinoma have been concentrated chiefly on producing palliation. In numerous cases there is no doubt that considerably more effective irradiation could have been given in the first cycle, which in general offers the best opportunity for success in treatment. One factor which, I am convinced, has contributed greatly to palliative and growth-restraining effects has been the choice of the size of the portal. As far as possible the portals have been restricted to a field large enough to include thoroughly only the estimated extent of the tumor, ignoring peripheral shadows on the roentgenogram thought to be caused by secondary atelectasis and inflammatory changes. This

restriction of portals renders possible the delivery of a greater dose to the tumor with less irradiation of surrounding tissue. In this connection, a considerable exercise of judgment is required in distinguishing between shadows probably mostly representing tumor, as in the case of some of the bulky solid carcinomas, and shadows merely representing peripheral atelectasis and secondary inflammatory changes. All the data at hand may be called on to aid in this judgment: the bronchoscopic findings, the films taken after the injection of lipiodol, the films made with heavy exposure, lateral and oblique films, and the finer features of the roentgen shadows.

Table XIV

BRONCHIOGENIC CARCINOMA
LIVING PATIENTS TREATED BY ROENTGEN RAYS

	Cases
12.5 years	1*
4.5 years	2
3 years	1
2 years	1
18 months	1
6 months	5
under 6 months	8
Total	19

Also one patient lost after 2 years was in good condition.

Duration of Life in the Surviving Patients (see Table xiv). Of the 20 living patients, one was operated on at New York Hospital, ten months ago, and is in good condition. The remaining 19 were all treated by roentgen rays. One, who also received some treatment by the radium pack, is alive for 12.5 years.* Two have survived over 4.5 years (and will probably soon pass the five year mark), one for three years, one for two years, one for eighteen months, 5 for six months, and 8 for less than six months. In addition, one patient lost track of since February, 1939, was in good condition when last seen.

As to the condition of these living patients, all who have passed the three year mark are up and about, apparently free of evidence of active cancer. The patient who has now survived 12.5 years had considerable necrosis of chest wall two and a half years ago, necessitating surgery and complicated later by empyema. She has recovered fairly well, however, from this complication.* The two year patient and the eighteen month patient are probably terminally ill. Of the patients with shorter duration, some are in excellent condition, some are ailing moderately, while others are apparently doomed not to survive much longer. Even in the cases of shorter duration, however, all but one showed some degree of palliation.

In surveying these living patients and considering only the five, four, three, and two year survival rates, the net results of irradiation of carcinoma of the lung seem rather disappointing; but an unbiased review of the palliations, some of remarkable degree, that have been witnessed in recent years leads to a belief that at present many more cases of carcinoma of the lung can actually be benefited by irradiation than by surgery at the time when a diagnosis can be made, and that a considerable improvement in results can be expected.

SUMMARY AND CONCLUSIONS

As a result of this study it is believed that aspiration biopsy is essential for the earlier diagnosis of a large proportion of cases of carcinoma of the lung, and that treatment of this disease by high voltage roentgen irradiation can accomplish a great deal in a palliative way, while possibilities of improved technique of irradiation promise considerably improved results in a disease which in the great majority of cases is not suitable for surgical intervention.

I am indebted to Dr. William L. Watson, who has performed most of the bronchoscopies in recent years in this group of cases; to Drs. C. S. Cameron and J. S. Binkley, for their assistance in compiling data from the case records; and to Edith H. Quimby, for her help in computing the tumor doses in roentgens.

* This patient died 9 months later (March 7, 1940).

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METASTATIC NEOPLASMS

A CLINICAL AND ROENTGENOLOGICAL STUDY OF INVOLVEMENT OF SKELETON AND LUNGS*

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INTRODUCTION

THE intelligent treatment and prognosis of malignant neoplasms is obviously dependent upon the recognition of tumor cells outside the confines of the primary tumor. Roentgenologic evidence has become a widely used supplement to clinical findings in searching for metastases. Since the skeleton and lungs are the most accessible of various parts of the body, they deserve particular attention in this connection. An understanding of the problem entails a close correlation of involved anatomical and pathological features.

In review, the principal types of spread encountered may be listed as follows: lymph-borne emboli; blood-borne emboli; lymph-vessel permeation; blood-vessel permeation; transcelomic spread and various combinations of these methods. One must bear in mind that although emboli and permeation usually occur in the orthograde direction, spread in the retrograde direction of vascular flow is extremely important following obstruction. The channels of spread are further complicated by extensive intercommunication. Gray[13] has recently shown that spread of cancer by lymph-vessel permeation is less common than was formerly supposed.

One or more of the above types of spread has been assumed in cases listed below as metastatic to the skeleton or lungs. Instances of pleural metastases are included with the lung groups. Instances of direct encroachment of the primary tumor into neighboring bone or lung have been avoided even though roentgenographic evidence is frequently similar.

MATERIAL

To accumulate data pertinent to the consideration of metastatic neoplasms, 1,803 hospital records and available corresponding roentgenograms have been reviewed. Only biopsy proved cases were considered. Among the entire series were 1,303 autopsied cases. All patients considered had been admitted to Pondville Hospital over a ten year period, prior to January 1, 1938. The percentage distribution of bone and lung metastases is furnished by tabulated findings in the autopsied cases. Although tables refer to autopsied cases only, the remarks concerning roentgenographic findings refer to both the autopsied and the other cases proved clinically.

Roentgenography of the lungs and major red bone marrow-bearing areas has been a policy of the Pondville Hospital for the study of all cases of malignant tumors in which clinical evidence suggested spread. In suspected and proved breast cancer this has been a routine procedure. The adequacy of such a film series was reported by Dresser and Pelletier[5] who found only one instance of bone involvement which would not have been shown in routine studies of the skull, spine, ribs, pelvis and proximal humeri and femora.

For presentation, cases have been arbitrarily arranged in 7 groups to facilitate consideration of various malignant conditions in their appropriate anatomical and pathological divisions.

Group I: Urinary Tract and Male Genital Organs.

There were 185 autopsied cases in this

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Fig. 1. Roentgenogram showing confluent osteolytic involvement of posterior right ilium and adjacent portion of sacrum from renal cell carcinoma. No other bone metastasis.

group (see Table 1). The primary organs involved were kidney, bladder, prostate, penis, testis and urethra.

Table I

URINARY TRACT AND MALE GENITAL ORGANS

Autopsies	Organs	Bone Metastases	Lung Metastases
		per cent	per cent
25	Kidney	20.0	40.0
46	Bladder	13.0	19.5
95	Prostate	57.8	28.4
10	Penis	.0	10.0
5	Testis	20.0	80.0
4	Urethra	25.0	25.0
185	Total	36.7	28.1

A. *Kidney.* Most of the 25 autopsied cases of primary renal tumors were renal cell carcinomas and hypernephromas arising in the cortex. Pulmonary metastases were present in 40 per cent and bone metastases were found in 20 per cent. These figures are similar to studies reported by a number of investigators in connection with frequency of bone and lung involvement.

Roentgenographic Findings. Many examples of solitary remote and apparently blood-borne metastases were found in both bones and lungs. Throughout the series a tendency to form solitary bone metastases often complicated by fracture was observed. Almost all the bone lesions were osteolytic (Fig. 1). Although lobulation of pulmonary metastases from renal tumors has been described,[23] it was not a dependable finding in the films reviewed. Of patients with Wilms' tumor, there was a much greater frequency of metastatic involvement of the lungs than of the bones.

B. *Bladder.* Forty-six autopsied cases of primary bladder cancer showed bone involvement in 13 per cent and lung involvement in 19.5 per cent. Of 79 autopsied cases collected by the Carcinoma Registry,[4] 58 were studied closely by postmortem, and metastatic foci were present in lungs in 25.8 per cent. Graves and Militzer[14] found osseous metastases in 11.86 per cent of 43 cases.

Roentgenographic Findings. Osteoblastic

Fig. 2. Roentgenogram showing osteoblastic metastases from carcinoma of bladder. No primary prostatic cancer.

metastases (Fig. 2) were encountered less frequently than osteolytic metastases secondary to malignant bladder tumors. This point is of interest because of the infrequent occurrence of bone-forming metastases secondary to tumors arising in stratified squamous or transitional epithelium. Livingston[22] has reported a similar experience. The pulmonary metastases were widely disseminated in some cases and relatively localized in others.

C. *Prostate.* In the 95 cases studied by autopsy, 57.8 per cent had bone metastases while only 28.4 per cent had lung metastases. The great predisposition of prostatic carcinomas to form osteoblastic metastases has been frequently recorded.[7] Extensive sectioning by Kaufman[19] resulted in demonstration of bone metastases in 72 per cent of his autopsied cases while Bumpus[2] using roentgenographic evidence alone found bone metastases in only 30 per cent of the cases. Graves and Militzer[15] found lung metastases in 8.6 per cent of cases studied for roentgenographic evidence of metastatic spread.

Roentgenographic Findings. The marked predominance of bone metastases over lung metastases secondary to prostatic cancer is a striking fact since the opposite distribution of metastases is true for most other large groups of primary tumors. Another consistent finding is the more frequent involvement of bones situated near the primary tumor. It seems that other tumors do not so closely obey the principle of direct increase in incidence of bone involvement with increasing proximity to the primary tumor in question. These facts regarding the prostate coincide with the observation of Warren,[27] *et al.* on the spread of lymph-borne tumor emboli along the proportionately numerous perineural lymphatic vessels which drain the prostatic area. Circuitous extension to the neighboring periosteal lymphatics furnishes opportunity for stimulation of bone formation and subsequent extension to medullary bone by means of cortical haversian canals. The presence of bone metastases in 33 autopsied patients of prostatic carcinoma who showed no accompanying lung involvement is obviously out of proportion to the remaining 1,208 autopsied cases of the series which showed only 71 instances of bone metastases without lung metastases. Schmorl[24] reported that prostatic bone metastases may indirectly produce calcium in the lung, presumably because the neoplastic cells incite osteosarcomatous growth in adjacent bone, such as vertebra and ribs. From this secondary metastatic focus embolic cells may produce osteoid tumors of the lung. Willis[31] states that stromal metaplastic transformation may occur from epithelial malignancies with the resulting possibility of calcium production in pulmonary metastases. However, in the present series, no calcium was detected in prostatic lung metastases. The problem of similarity between advanced metastatic involvement of the pelvis and Paget's disease was encountered several times; however, the discrete osseous metastatic nodules of the former furnish quite a contrast to the accentuated bone trabeculae of condensing disseminated osteoporosis. A significant point regarding the lytic bone metastases of prostatic carcinoma was their greater frequency in the more remote bones, particularly in patients who showed lung metastases and hence, presumptive evidence of blood-stream dissemination.

D. *Penis.* Of 10 cases of primary carcinoma of the penis, only one, or 10 per cent, had secondary pulmonary involvement. None had osseous involvement.

Roentgenographic Findings. The pulmonary metastases presented no unusual characteristics.

E. *Testis.* There were 5 autopsied cases in this group of which 4 showed lung involvement and one bone involvement. Twenty-six inoperable clinical cases not autopsied showed roentgenographic evidence of metastases in 53.9 per cent to lung and 15.3 per cent to bone. Stout[25] names lymph nodes, lungs, liver and bones in order of frequency of metastatic involvement.

Roentgenographic Findings. Bone metastases were unanimously osteolytic and showed no greater tendency to involve pelvis and lumbar spine than other red bone marrow-bearing portions of the skeleton. In one instance a lytic lesion, several centimeters in diameter, was present in the frontoparietal region with complete destruction of both tables of the calvarium. The lung metastases tended to reach the stage of huge nodulation in many patients. Incidentally, patients treated for lung metastases from the testis as a group showed the greatest radiosensitivity of all tumors metastatic to the lungs.

F. *Urethra.* Of 4 primary carcinomas, one showed postmortem evidence of pulmonary metastases and one showed osseous metastases.

Roentgenographic Findings. Scattered pulmonary nodules were shown in the roentgenogram. The bone metastases were osteolytic.

Comment. Of the entire group of 185 autopsied cases of cancer in urinary tract and male genital organs, 36.7 per cent showed osseous metastases and 28.1 per cent pulmonary metastases. As mentioned above, the predominance of bone involvement over lung involvement may be attributed to the pronounced extension of prostatic metastases to neighboring bones through the lymphatics. The greater frequency of bone involvement in the absence of lung involvement in prostatic cancer further points to the importance of lymphatic extension. In this connection, the production of osteoblastic metastases from both bladder and prostate suggests a constant influence of lymphatic drainage.

Group II: Female Genital Organs.

This group (Table II) includes 160 cases of vulvar, cervical, fundal, ovarian and vaginal primary cancers.

A. *Vulva.* Of 10 autopsied cases of cancer of the vulva, 2 showed pulmonary metastases; none showed osseous metastases. Review of the literature produced no reported large series of cases.

Roentgenographic Findings. Chest films showed no distinctive characteristics of the metastases in the lungs.

B. *Cervix.* Of 99 autopsied cases, bone involvement was present in 8 per cent and lung involvement in 18.1 per cent. In 132 cases, Warren[28] found bone metastases in 3.94 per cent and lung metastases in 15.1 per cent. All bone metastases were osteolytic. A much higher relative percentage of lung and bone metastases were found in histologically Grade 3 cases than in Grades 2 and 1.

TABLE II

FEMALE GENITAL ORGANS

Autopsies	Organs	Bone Metastases	Lung Metastases
		per cent	per cent
10	Vulva	.0	20.0
99	Cervix	8.0	18.1
32	Fundus	.0	43.7
17	Ovary	6.0	12.0
2	Vagina	50.0	50.0
160	Total	6.2	23.1

Roentgenographic Findings. All of the above bone metastases were osteolytic. There was no striking correlation of the proximity of the metastases to the primary tumor site. The preponderance of spread to bones containing large amounts of red marrow was a definite finding. An interesting example of joint cartilage and capsule acting as a barrier to joint invasion was noted in a patient who showed extensive lytic destruction of the adjacent proximal portion of the tibia (Fig. 3). Varying types of pulmonary metastatic nodules were present in this group.

C. *Fundus.* Fourteen of 32 autopsied cases of cancer primary in the uterine fundus were found to have pulmonary metastases. No bone metastases were encountered in this relatively small group of cases, however in several cases observed clinically, roentgenograms showed bone metastases. It is interesting that metastases from adenoacanthomas were present in both lungs and bones.

Roentgenographic Findings. The bone metastases which were present were all osteolytic. Instances of pathological fracture were observed. The lung metastases showed no distinctive characteristics.

D. *Ovary.* In 17 autopsied cases of ovarian cancer, 12 per cent showed lung metastases and 6 per cent bone metastases. Ewing[8] recorded blood-borne pulmonary metastases in 5 to 7 per cent and bone involvement in a somewhat smaller percentage.

Roentgenographic Findings. A clinically observed case showed remote bone metastases near the entrance of the principal nutrient artery of the femur. One case showed pulmonary apical metastatic involvement with late autogenous phrenic interruption. A clinically observed primary ovarian tumor metastatic to the vertebrae showed herpes zoster of a corresponding level indicative of posterior root invasion.

E. *Vagina.* Of 2 primary vaginal carcinomas, one showed metastatic extension to the bones and one to the lungs. The literature contains few reports regarding the spread of this tumor.

Roentgenographic Findings. No distinctive characteristics were encountered roentgenographically. The bone metastases were osteolytic.

Comment. Of the entire group of autopsied patients with primary cancer of the female genital organs, 6.2 per cent metastasized to bone and 23.1 per cent to lungs. Regarding bone lesions, it is significant that all were osteolytic and of a distribution compatible in a majority of cases with blood-borne embolic origin.

Group III: Oral cavity.

Malignant primary lesions of the lip, alveolar ridge, buccal mucosa, floor of mouth, palate, tongue, tonsil and pharynx were considered in a third group (Table III). Two hundred and eighteen of these cases have been autopsied. As above mentioned, direct infiltrating growth of the primary tumor into bone constitutes a different type of problem. Such occurrences have not been tabulated as metastatic.

Fig. 3. Roentgenogram showing preservation of knee joint despite extensive involvement adjacent to it. Primary epidermoid carcinoma of cervix.

A. *Lip.* Thirty-eight autopsied cases showed osseous metastases in 5.2 per cent. Lung metastases were found in 2.6 per cent. Review of the literature reveals that remote metastases from primary cancer of the lip are quite rare.

Table III

ORAL CAVITY

Autopsies	Organs	Bone Metastases	Lung Metastases
		per cent	per cent
38	Lip	5.2	2.6
10	Alveolar ridge	.0	.0
30	Buccal mucosa	.0	10.0
20	Floor of mouth	.0	5.0
14	Palate	7.0	7.0
59	Tongue	.0	23.7
21	Tonsil	.0	9.0
26	Pharynx	4.0	15.4
218	Total	1.8	11.9

Roentgenographic Findings. The bone metastases both in autopsied cases and in clinically proved cases were osteolytic in character and remote in situation. An example was the presence of a fracture at the site of a lytic metastasis in the posterior portion of a rib. The lung metastases showed no unusual roentgenographic features.

B. *Alveolar Ridge.* Of 10 autopsied cases of tumors which arose from the epithelium over the alveolar ridges, no metastatic involvement of the lungs, pleura, or skeleton could be found.

C. *Buccal Mucosa.* Bone metastases were absent in 30 patients who died of primary lesions of the buccal mucosa. Ten per cent showed lung metastases.

Roentgenographic Findings. Pulmonary metastases were not distinctive in appearance. One patient showed a pleural effusion evidently the result of metastases.

D. *Floor of Mouth.* Of 20 autopsied cases, one patient showed pulmonary metastases. There was no instance of metastatic bone involvement.

Roentgenographic Findings. Disseminated, small pulmonary nodules were observed.

E. *Palate.* Fourteen autopsied cases of primary malignant neoplasms in the palate gave pulmonary metastases in 7 per cent and bone involvement in 7 per cent or one each.

Roentgenographic Findings. Disseminated pulmonary nodules and osteolytic bone involvement were observed. A compression fracture of a dorsal vertebral body was one example of metastatic involvement of bone. A palatal lesion metastatic to the right cervical nodes was found to have produced right pleural metastases which were obscured by pleural thickening from a large lung abscess.

F. *Tongue.* A series of 59 autopsied cases included no instance of bone involvement. Lungs and pleura were involved in 23.7 per cent of cases. Ewing[9] has observed repeated metastases from the tongue to the liver, lungs, pleura, heart and adrenal. Willis[32] found 5 per cent bone and 35 per cent lung involvement. Fuendeling and Hunnicutt[12] found 11.5 per cent of 26 autopsied cases with lung and pleural metastases and 7.8 per cent with bone. The 26 cases were tongue malignancies included in a summary of 1,000 consecutive autopsies of various primary malignant conditions observed at Stanford University Hospital.

Roentgenographic Findings. A relatively high percentage of pleural effusions was found with the disseminated pulmonary metastases.

G. *Tonsil.* In 21 autopsies, no osseous metastases from primary tonsillar cancer were encountered. Lungs were involved in 9 per cent.

Roentgenographic Findings. Metastatic pulmonary nodules presented no unusual characteristics.

H. *Pharynx.* Of 26 primary carcinomas arising in the oropharynx, osseous involvement was encountered in 4 per cent and pulmonary involvement in 15.4 per cent. The Stanford series[12] included 16 cases with metastases to lungs in 12.5 per cent and to bones in 25 per cent.

Roentgenographic Findings. Bone lesions were osteolytic. Lung metastases were not characteristic.

Comment. In this group of 218 patients, the incidence of bone metastases (1.8 per cent) and of lung metastases (11.9 per cent) is less than from any other group of primary tumors. Hence, extensive roentgenographic investigation may well be reserved for patients who present advanced disease. The relative frequency of pleural metastases even in the absence of pulmonary nodules suggests that lymphatic spread to pleura must often be a factor. To the present, we have seen only osteolytic bone metastases from this group of cases. Willis[33] in 62 cases of primary epidermoid carcinomas found 6.5 per cent metastatic to bones in autopsied cases.

Group IV: Gastrointestinal System.

Autopsied cases of primary neoplasms in the esophagus, stomach, biliary tract, pan-

creas, large bowel and small bowel contributed 391 cases in this general group (Table IV).

TABLE IV

GASTROINTESTINAL TRACT

Autopsies	Organs	Bone Metastases	Lung Metastases
		per cent	per cent
56	Esophagus	1.8	25.0
107	Stomach	7.4	16.8
21	Biliary tract	.0	14.2
16	Pancreas	6.3	25.0
188	Large bowel	11.1	21.2
3	Small bowel	.0	33.0
391	Total	7.9	20.5

A. *Esophagus.* Of 56 cases, 1.8 per cent showed osseous metastases while 25 per cent showed metastatic extension to the lungs and pleura. Klein[21] found vertebral metastases in 1.75 per cent of autopsied cases. Among 83 autopsied cases it was found that 9.6 per cent were metastatic to lungs and pleura and 2.4 per cent to bones in the Stanford series.[12]

Roentgenographic Findings. Although various types of pulmonary and pleural metastases were observed among autopsied and other cases, one of the most striking examples of miliary distribution of metastases was in this group (Fig. 4).

B. *Stomach.* One hundred and seven primary malignant tumors of the stomach on autopsy showed bone metastases in 7.4 per cent and lung metastases in 16.8 per cent. Kerr and Berger,[20] in an extensive presentation and discussion of bone metastases in carcinoma of the stomach, found variations of from 1 to 22 per cent reported by various authors from clinical and autopsy surveys. The most frequent sites of involvement were found in the spine, ribs, femora, sternum, pelvis, humeri, skull and sacrum. In 200 autopsied cases of the Stanford series,[12] bone metastases were found in 2 per cent and metastases to lungs and pleura in 29 per cent.

Roentgenographic Findings. Included examples of osteolytic and osteoblastic bone metastases were almost evenly distributed. In one instance, a metastasis had grown a remarkable amount locally to produce destruction of a portion of the rib, marked invasion of the pleura and infiltration of the adjacent lung. Pulmonary metastases were nodular in character, not distinctive in appearance.

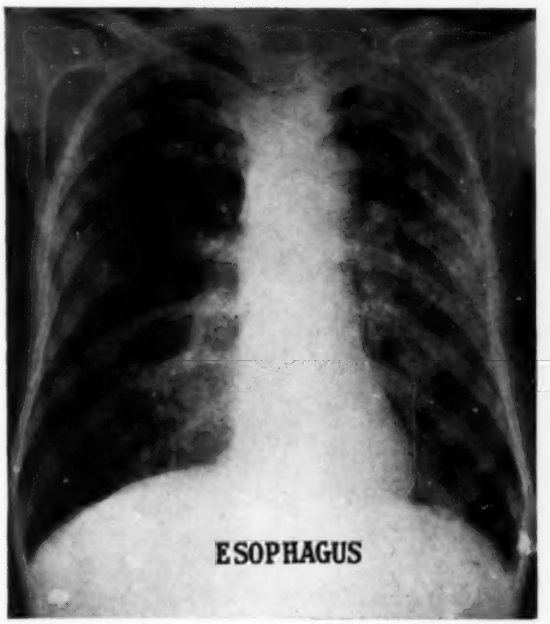

FIG. 4. Roentgenogram demonstrates miliary distribution of metastatic lesions from primary epidermoid carcinoma of the esophagus. No tuberculosis or silicosis discovered at autopsy.

C. *Biliary Tract.* Of 21 autopsied cases of primary cancer in the biliary tract, 14.2 per cent metastasized to the lungs. No bone metastases were found. A clinically observed case in a young female presented a mixed osteoblastic and osteolytic lesion in the proximal portion of the right femur.

Roentgenographic Findings. Pulmonary nodules and pleural involvement were not distinctive in character. The mixed metastatic lesions of the femur mentioned above was predominantly lytic.

D. *Pancreas.* Sixteen autopsied cases showed bone metastases in 6.3 per cent and lung metastases in 25 per cent. Fuendeling and Hunnicutt[12] found extension to lungs and pleura in 45 per cent of their cases. They reported bone involvement in 7.3 per cent.

Roentgenographic Findings. Metastatic lesions in ribs, vertebrae, and other bones were osteolytic. Compression vertebral fractures were observed. In one case marked mediastinal broadening was accompanied by metastatic pulmonary nodules and rib invasion.

E. *Large Bowel.* One hundred and eighty-eight autopsied cases showed bone metastases in 11.1 per cent; lung metastases in 21.2 per cent. In several instances, preliminary roentgenographic evidence resulted in special attention at autopsy to bones not usually included in the routine postmortem examination. Of 156 cases of large bowel malignancy, Warren[29] found 1.2 per cent metastatic to bones and 16.6 per cent metastatic to lungs. Aufses[1] found 8 patients with bone metastases in a group of 117 autopsies. Of 141 cases in the Stanford series,[12] 2.8 per cent metastasized to bone and 16 per cent to lung and pleura.

Roentgenographic Findings. Among bone metastases it is of interest to note that from primary rectal carcinomas, mixed metastatic lesions of pubic rami in 2 instances produced roentgenographic evidence which *per se* would have been interpreted as osteogenic sarcoma. The bone involvement was predominantly osteolytic. Nodules of varying sizes were found in the lungs in many cases. A case secondary to cancer of the rectum exemplified the consolidated type of pneumonic metastasis in the medial portion of the right lower lobe.

F. *Small Bowel.* Only 3 autopsied cases of primary cancer of the small bowel were found. No metastatic involvement to bone occurred. In one case lung metastases were present.

Roentgenographic Findings. No roentgenograms were available to show the involved lungs.

Comment. The 391 autopsied cases which contributed to this group showed bone metastases in 7.9 per cent and lung metastases in 20.5 per cent. Osteolytic lesions were the predominant type of bone involvement and in general showed only the predisposition of location of red bone marrow. Similarity to osteogenic sarcoma was striking in 2 instances. The lung metastases were of many types. Contrasting types varied from miliary distribution to confluent pneumonic infiltration.

Group V: Respiratory System.

Included in this group were 96 autopsied cases of primary neoplasms of nasopharynx, larynx, lungs, trachea and sinuses (Table v).

Table V

Respiratory Tract

Autopsies	Organs	Bone Metastases	Lung Metastases
		per cent	per cent
8	Nasopharynx	37.5	25.0
41	Larynx	2.4	17.0
33	Lungs and trachea	24.2	45.4
14	Sinuses	7.1	21.4
96	Total	13.5	28.1

A. *Nasopharynx.* Both in the 8 autopsied cases and in a larger number of clinically observed cases not autopsied, a high percentage of remote metastases occurred. Many of the tumors of this group were examples of undifferentiated primary neoplasm with early and extensive metastases. Of the 8 autopsied cases, 3 showed involvement of osseous structures and 2 had extended to lungs.

Roentgenographic Findings. A typical example of metastatic involvement in bone was noted in the case of a lytic lesion of the sternum. No osteoblastic metastases occurred. There was no discernible relation of the proximity of bone metastases to the site of primary tumor; in fact, the majority occurred distal to the dorsal region. The lung metastases were almost all discrete nodules of varying size.

B. *Larynx.* Forty-one autopsied cases of laryngeal cancer showed an incidence of spread to bone in 2.4 per cent and to lung in 17 per cent. Burke[3] found no bone metastases in 23 autopsied cases and lung metastases in 8.5 per cent. Burke's study of metastases from squamous cell carcinoma furnished further demonstration of the

tendency of poorly differentiated carcinomas to metastasize frequently in comparison to well differentiated tumors.

Roentgenographic Findings. Bone metastases were found to be osteolytic. Lung metastases presented no distinctive characteristics.

C. *Lungs and Trachea.* Of 33 autopsied cases, bone metastases were found in 24.2 per cent. Lung metastases were found in 45.4 per cent. Huguenin[18] quoted various authors to supply the information that remote metastases to some part of the body occurred in 50.8 to 99.7 per cent of cases. Other portions of the lungs, the liver, the brain, and bones have been shown to be the most frequently affected sites. In comparing primary and metastatic lung cancer, Farrell[11] found atelectasis, massive tumor, pleural effusion, hemoptysis and respiratory symptoms to be more frequent in the primary cases.

Roentgenographic Findings. Both osetolytic and osteoblastic bone metastases were observed with a marked tendency to occur in the thoracic cage. Metastases to lobes other than the site of origin of the primary were quite frequent. Pleural metastases were also frequent. Epidermoid and adenocarcinoma showed similar behavior.

D. *Sinuses.* Of 14 autopsied cases, 7.1 per cent metastasized to bone and 21.4 per cent to lungs. Burke[3] found one example of lung metastases and one of bone metastases among 3 autopsied cases.

Roentgenographic Findings. Bone metastases were osteolytic. Lung metastases presented no distinctive characteristics.

Comment. Of this entire group of 96 malignant respiratory tract tumors, 13.5 per cent metastasized to bone and 28.1 per cent to lungs. In general, it might be said that this frequency of spread justifies more complete roentgenographic observation than is usually conducted.

Group VI: Neuromuscular and Skeletal Systems.

This group included a total of 58 autopsied cases representing primary malignant lesions of the bone, fibrosarcoma, liposarcomas, malignant melanomas and malignant tumors arising in the nervous tissues (Table VI).

TABLE VI

NEUROMUSCULAR AND SKELETAL

Autopsies	Organs	Bone Metastases	Lung Metastases
		per cent	per cent
22	Bone tumors	59.0	50.0
11	Fibro- and liposarcomas, etc.	16.1	54.5
16	Malignant melanomas	43.7	62.5
9	Nervous system	11.1	11.1
58	Total	39.6	48.2

A. *Bone Tumors.* Of 22 autopsied cases, 59 per cent showed metastases to parts of the skeleton other than the site of origin of the primary. Although this metastatic tendency to other bones was more pronounced in Ewing's tumors, it was found on multiple occasions in osteogenic sarcomas. Fifty per cent of cases showed lung metastases. Willis[34] found one example of metastatic involvement in a remote bone from primary osteogenic sarcoma of the right femur among 4 autopsied cases of this particular malignancy.

Roentgenographic Findings. Metastases to other bones were both osteolytic and osteoblastic in type. The most significant point regarding lung metastases was the occasional formation of calcium in metastatic nodules; presumably, those metastases which were of relatively long duration (Fig. 5). This calcification was not observed in metastases from Ewing's sarcoma to the lungs. Willis[34] found multiple ossifying lung metastases in 1 of 4 autopsied cases.

B. *Fibrosarcomas and Liposarcomas.* In a group of 11 cases, bone metastases were observed in 18.1 per cent and lung metastases in 54.5 per cent. Other tumors of this general group, particularly myxosarcomas and hemangio-endotheliomas were observed to produce frequent lung metastases and less frequent bone metastases. This was

Fig. 5. Roentgenogram showing calcium production of lung metastases. Patient lived nine years following removal of primary osteogenic sarcoma. Steady increase in calcium formed in metastases over period of several years.

of interest because of occasional histologic difficulty in recognizing potentiality for spread in the latter tumor.

Roentgenographic Findings. Bone lesions secondary to connective tissue sarcomas were osteolytic. Pulmonary metastases were often massive irregular nodules as much as 8 to 10 cm. No ossification of metastatic nodules was observed in this group.

C. *Malignant Melanomas.* In this group of 16 autopsied patients, bone metastases occurred in 43.7 per cent and lung metastases in 62.5 per cent.

Roentgenographic Findings. Bone lesions were all osteolytic and showed the distribution tendency of major red marrow containing bones. Lung metastases were unusually disseminated and frequently involved all lobes of both lungs. Metastases were found occasionally after the primary lesion had been quiescent for years.

D. *Nervous System.* Of 9 autopsied cases consisting of neuroblastomas, neurogenic sarcomas and chordomas, an example of pulmonary metastases was found and one of bone involvement. Willis[35] found no remote metastases from various primary intracranial tumors. In 2 neuroblastomas, he found lung metastases, one of which also had bone metastases.

Roentgenographic Findings. All bone metastases observed in this group and clinically observed cases were osteolytic in character. A neurogenic sarcoma of the palate by lytic metastatic involvement resulted in a compression fracture of a vertebral body. Lung metastases were most prominent in cases of neuroblastoma of the adrenal medulla. Pleural involvement was seen.

Comment. Of the entire foregoing group of 58 patients, bone metastases were found in 39.6 per cent and lung metastases in 48.2 per cent. Occasionally the intrinsic property of a lung metastasis furnished a clue regarding the nature of the primary tumor. An example of this is found in some of the calcium containing lung metastases from primary osteogenic sarcomas. The film contrast between homogeneous pulmonary metastases from connective tissue tumors and the variable density of those from carcinomas was found to be unreliable in the cases observed in this entire study.

Group VII: Glandular and Hemopoietic Systems.

One hundred and ninety-five autopsied cases supplemented other biopsy proved clinical cases to provide material for this group (Table VII).

Table VII

GLANDULAR AND HEMOPOIETIC

Autopsies	Organs	Bone Metastases	Lung Metastases
		per cent	per cent
105	Breast	57.1	62.0
8	Thyroid	37.5	60.0
7	Parotid	28.5	42.8
61	Lymphomas	31.1	32.7
8	Leukemias	75.0	12.5
6	Branchiogenic	16.6	50.0
193	Total	46.6	49.7

A. *Breast.* Of 105 autopsied cases, bone metastases were found in 57.1 per cent and lung metastases in 62 per cent. Of 162 cases, Warren and Witham[30] found 58 per cent metastatic to lungs and 42.6 per cent metastatic to bones. Of 69 cases, metastatic to bone, 41 showed pulmonary metastases. This and other facts resulted in the conclusion that most osseous metastases from the breast are hematogenous. Handley[17] found pleural involvement in 38 per cent of the cases. Gross[16] found pleural involvement in 50.9 per cent, lungs in 49.9 per cent and bones in 20.5 per cent. Of 393 metastases from breast carcinomas, 95.4 per cent were osteolytic according to Sutherland,[26] *et al.* Extensive dissemination of breast cancer by lymph-vessel permeation as reported by Handley[17] seemed difficult to verify in that such cases were shown by autopsy to present blood-steam invasion.

Roentgenographic Findings. Bone metastases were of osteolytic, osteoblastic and mixed types. It was of interest that secondary to an "inflammatory" carcinoma of the breast, a previously negative roentgenographic series was followed in three months by a series showing widely disseminated and advanced lytic metastases. Metastatic lung nodules were not distinctive in appearance and were of varying forms. Pleural metastases as indicated by soft tissue prominence following pleural outlines and by the presence of hydrothorax were found in many patients on the same side as was the primary breast tumor and was evidently the result of lymphatic spread. Six breast sarcomas showed in general similar distribution.

B. *Thyroid.* Eight autopsied cases showed metastatic involvement of bones in 37.5 per cent and of lungs in 60 per cent. Various estimates gathered from the literature regarding frequency of bone metastases range from 6 to 70 per cent.

Roentgenographic Findings. Bone metastases were unanimously osteolytic. An example was found in destructive involvement of the right femur in its proximal portion complicated by fracture. Metastatic nodules in the lungs presented no distinctive characteristics.

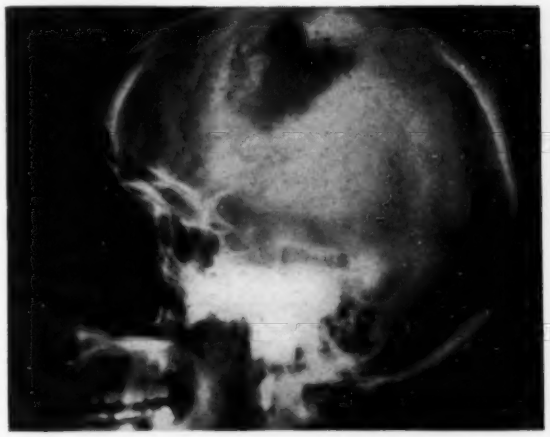

Fig. 6. Roentgenogram showing osteolytic lesion of Hodgkin's disease in parietal bone.

C. *Parotid.* Seven autopsied cases showed an incidence of 28.5 per cent bone metastases and 42.8 per cent lung metastases.

Roentgenographic Findings. Bone metastases were all of the lytic type. There was no significant distribution of bone lesions, a good example of which was the presence of a very large lytic area in the ilium. Pulmonary metastases were predominantly large nodules.

D. *Malignant Lymphoma and Hodgkin's Disease.* Of 61 autopsied cases, bone involvement was encountered in 31.1 per cent (Fig. 6) and intrapulmonary involvement was present in 32.7 per cent. An early report of bone involvement was that of Dresser[6] who in 1926 found more than 4 per cent in cases of Hodgkin's disease. This finding was further confirmed by his later observations. Ewing[10] points to the metastatic character of the growth in the lungs and elsewhere secondary to Hodgkin's disease as evidence for its classification as a malignant neoplasm.

Roentgenographic Findings. The majority of bone lesions were osteolytic although some calcium formation was observed. Recalcification of an osteolytic lesion of the clavicle occurred ten months after roentgen treatment. A neoplastic fracture of the femoral shaft occurred in a patient proved

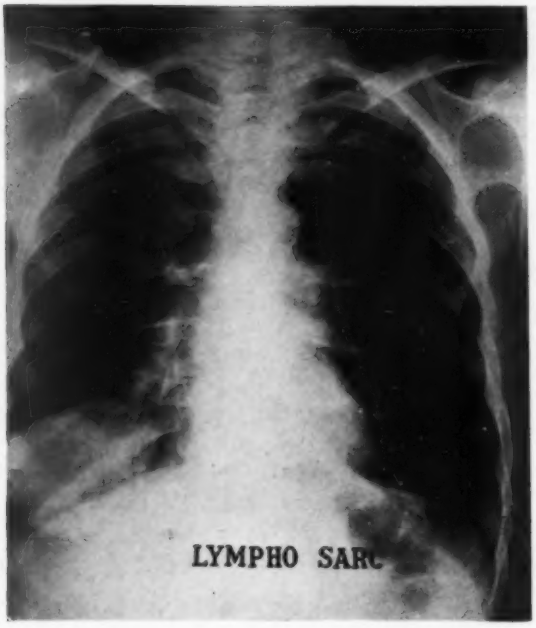

Fig. 7. Roentgenogram showing large discrete intrapulmonary nodule in lymphosarcoma.

to have lymphosarcoma. Several cases showed solitary discrete nodules in the lung periphery, some measuring as much as 8 cm. in diameter (Fig. 7).

E. *Leukemias.* Of 8 autopsied cases, 6 were found at postmortem to show leukemic change in cortical bone. One patient showed leukemic infiltration of the peripheral lung tissues.

Roentgenographic Findings. No roentgenographic evidence of leukemic change was recognized.

F. *Branchiogenic Tumors.* Six patients of this group showed lung metastases in 50 per cent and bone metastases in 16 per cent.

Roentgenographic Findings. Lytic bone lesions were present in the one autopsied case. Lung metastases presented no distinctive characteristics.

Comment. In this group of 195 autopsied cases, lung metastases occurred in 49.7 per cent; bone metastases in 46.6 per cent. The breast constitutes the most potentially metastatic producing single organ of the entire study. The lymphomas metastasized frequently enough to warrant careful observation. Roentgenographic evidence is unreliable for the study of leukemic involvement of the bone cortex.

SUMMARY

Of the 1,303 autopsied cases (Table VIII), 35.3 per cent showed gross or microscopic evidence of extension to lungs or bones. Of these, 26.6 per cent of cases showed lung metastases while 18.4 per cent showed bone involvement. The greater frequency of pulmonary involvement coincides with the position of the lungs as filtering organs. On the other hand, 104 patients had bone metastases in the absence of lung metastases. Such evidence obviously justifies the careful study of bones for metastases even when the chest is uninvolved. The great variety of distribution of metastases can be explained only on the basis of a combination of circumstances. Autolysis of a small or great percentage of cells may occur as they are being transported, or, cells may fail to survive where they lodge, or cells may remain quiescent never to establish focal invasive growth. The transpulmonary passage of tumor cells is undoubtedly a possibility even when foci of neoplasm cannot be demonstrated in the lungs. The unquestionable filtering power of the lungs, liver and regional lymph nodes exerts an influence on the eventual distribution of

Table VIII

SUMMARY

Autopsies	Systems	Bone Metastases	Lung Metastases
		per cent	per cent
185	Urinary tract and male genital organs	36.7	28.1
160	Female genital organs	6.2	23.1
218	Oral cavity	1.8	11.9
391	Gastrointestinal tract	7.9	20.5
96	Respiratory tract	13.5	28.1
58	Neuromuscular and skeletal	39.6	48.2
195	Glandular and hemopoietic	46.6	49.7
1303	Total	18.4	26.6

metastatic cells. Still another factor is the consistent predilection of certain primary tumors for certain remote organs, best explained on the basis of intrinsic affinity of given tumor cells for certain tissue.

In the entire series of 1,803 patients, roentgenographic evidence indicated a definite correlation of bone metastases with the anatomical distribution of red bone marrow, i. e., most metastases were found in bones which contained the most red marrow. Prostatic metastases alone seemed to bear a dependable relation to the proximity of the primary tumor, i. e., the nearer the primary, the higher the incidence of bone involvement.

Most metastatic lesions in bone are osteolytic in character. In the present series it seems significant that in no case could an osteoblastic bone metastasis be found secondary to primary malignancy arising in stratified squamous cell epithelium. There were a few instances of bladder (transitional epithelium) malignancies which caused osteoblastic metastases. The osteoblastic metastases in this connection may be related to spread predominantly by perineural lymphatics to periosteal lymphatics.

A tendency was observed for renal neoplasms to produce solitary metastases. Such distant blood-borne metastases were frequently related to a neighboring nutrient vessel entrance.

Roentgenograms subsequent to radiation treatment of osteolytic lesions were found to show calcification more often if the metastasis was definitely radiosensitive than otherwise.

A striking relative immunity of joints in the presence of extensive adjacent neoplastic involvement was frequently observed. This undoubtedly results from the action of the joint cartilage and capsule as barriers to invasion.

In some instances, an increased sedimentation rate and tendency to macrocytic anemia coincided with film evidence of advanced metastatic involvement of bone.

Discrete pulmonary nodules from various forms of lymphoblastoma were not infrequent in available films of these cases. These nodules were solitary in some cases and disseminated in others. A definitely greater frequency of pleural extension was found in primary tumors arising above the diaphragm, including head and neck, as compared to those arising below the diaphragm. Many times, cancer of the breast was accompanied by pleural extension on the same side without discrete pulmonary metastases.

The most dependable intrinsic characteristic of pulmonary metastasis was the presence of calcium in occasional instances where lung involvement was of long duration and primary tumor was osteogenic in origin. Ewing's tumor, because of its different nature, caused no calcium formation in chest metastases.

CONCLUSIONS

1. Skeletal and pulmonary metastases have been considered in 1,803 patients in an attempt to further orient the present use of roentgenological investigation.

2. Bone metastases were distributed in essentially direct proportion to the amount of regional red bone marrow rather than the increasing proximity of the primary with the notable exception of those from the prostate.

3. Blood-borne osseous metastases in the absence of lung metastases were of sufficient frequency to emphasize the present clinical trend to search the skeleton for metastases even though the lungs may be negative.

4. Except for a minority of bladder cancers, no tumors arising from stratified squamous or transitional epithelium produced osteoblastic metastases.

5. In several cases, positive demonstration of calcium in lung metastases coincided with the existence of osteogenic primary neoplasms.

6. Of malignant conditions arising in nervous tissue, only neuroblastomas, chordomas, neurogenic sarcomas and retinal gliomas produced either skeletal or pulmonary metastases. No bone or lung metas-

tases were observed from primary brain tumors.

7. Greater cognizance is due the fact that various forms of lymphoma may produce discrete intrapulmonary nodules with or without mediastinal and hilar disease.

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TOMOGRAPHIC STUDY OF CANCER OF THE LARYNX[1]

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THE progress in the treatment of cancer of the larynx has brought about a better knowledge of its clinical aspects and a more accurate conception of the point of origin of the tumor and of its extent before any treatment is decided upon.

The laryngoscopic examination remains the basis of the diagnosis but it does not always give an idea of the real extent of the invasion of the tumor. Also, in some cases the laryngoscopic examination may, for some reason, be difficult and give little information.

In 1922, Coutard[2] devised and developed the roentgenographic examination of the pharynx and larynx by means of a profile plate. This has been of great value in determining the extent of tumors of the hypopharynx. In the larynx the profile roentgenogram is very useful in tumors of the anterior subglottic region, of the laryngeal wall of the epoglottis, and of the

FIG. 1. Frontal tomogram of a normal larynx, showing the free edge of the epiglottis with both pharyngo-epiglottic folds (above), the two descending aryepiglottic folds, false cords, Morgagni's ventricles, both vocal cords, subglottic and tracheal lumen.

FIG. 2. Drawing of Figure 1. The glottic and supraglottic lumen resembles a club of playing cards. Externally the pyriform sinus and then the thyroid cartilage (in black). Below (also in black) on both sides of the first portion of the trachea, the cricoid.

[1] Read before the Philadelphia Chapter of the Pan-American Medical Association, April 5, 1939.
[2] Coutard. Note preliminaire sur la radiographie du larynx normal et du larynx cancereux. *J. belge de radiol.*, Vol. 13, p. 287.

Fig. 3. Tumor of Morgagni's ventricle invading the false cord, the vocal cord and the subglottis of the same side.

Fig. 4. Frontal tomogram of same case as Figure 3, showing invasion extending from false cord to subglottic and narrowing externally the pyriform sinus.

anterior commissure—in other words, in those tumors in which the development is more important on a sagittal plane. In contrast to this, these profile projections are not of great value in determining the extent of tumors of the false cord, lateral subglottis—in other words, tumors in which the development follows a frontal plane.

Several attempts have been made to obtain frontal roentgenograms of the larynx; the superposition of the spine was the first obstacle. The technique which consisted in

Fig. 5. Tumor of the epiglottis treated by surgery. Recurrence on right false cord and arytenoid.

the introduction of a narrow film down to the mouth of the esophagus does not have any practical value.

In 1936, I started working with the tomographic examination of the larynx[3]

[3] *An. d. aten. de clin. quir.*, July, 1936.

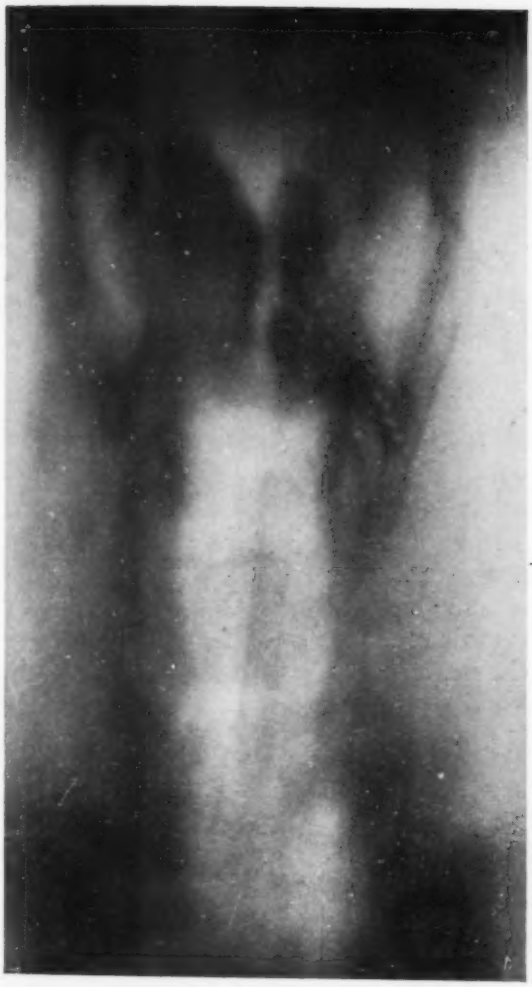
Legends for Figures 6–9 on next page.

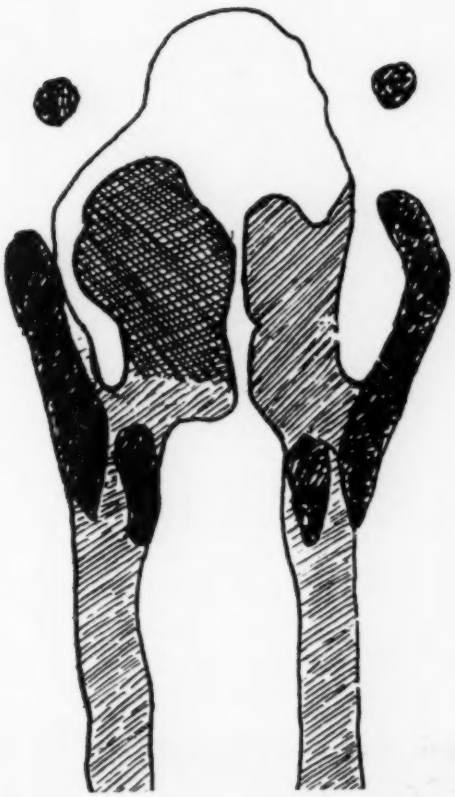
Fig. 6 (*upper left*). Tomogram of same case as shown in Figure 5. Laryngeal lumen altered. The heavy shadow of the tumor is evident.

Fig. 7 (*upper right*). Drawing of Figure 6.

Fig. 8 (*lower left*). Frontal tomogram of an advanced case of tumor of the false cord.

Fig. 9 (*lower right*). Drawing of Figure 8.





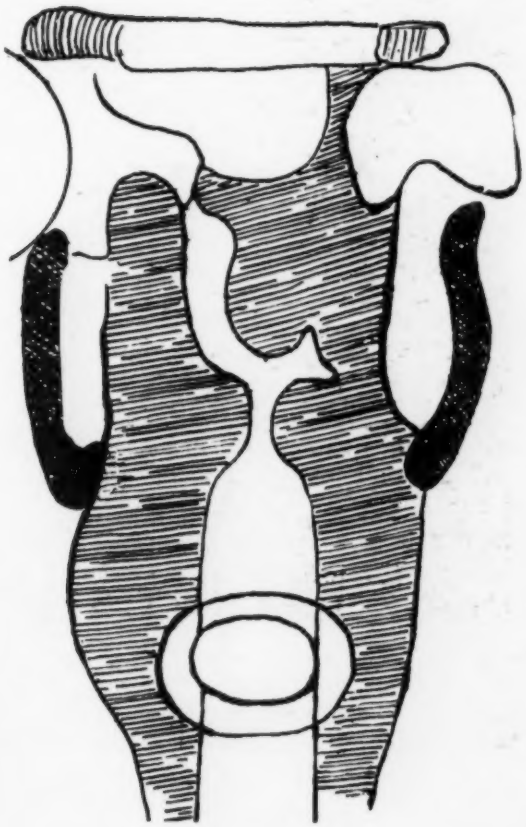


Fig. 10. Tumor of right false and true cords on a tuberculous larynx.

and the results were encouraging. The tomograph seems to solve the problem of the frontal view of the larynx by furnishing an anatomo-roentgenographic frontal section which is of great value in determining the extent of tumors of the false cords, ventricles, glottic and subglottic regions.

Tomography does not replace any of the previous methods of examination of the larynx, but rather complements them.

In the course of our study of tumors of the larynx we have had the opportunity of considering a few cases of laryngocele or hernia of Morgagni's ventricle. In those cases tomography seems to be of diagnostic value, especially in the cases where the hernia remains in the larynx and may simulate a tumor. Tomography shows the pres-

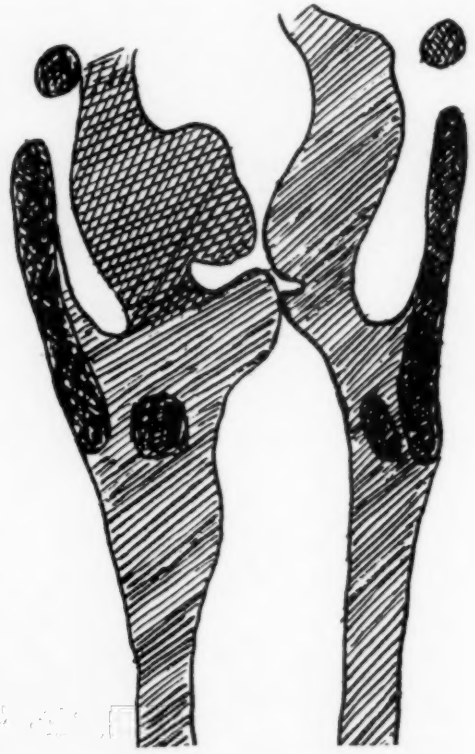


Fig. 12. Drawing of Figure 11.

Fig. 11. Frontal tomogram showing enlargement of right false and true cords, narrowing of the ventricle. Left ventricle almost invisible due to edema as confirmed by intervention.

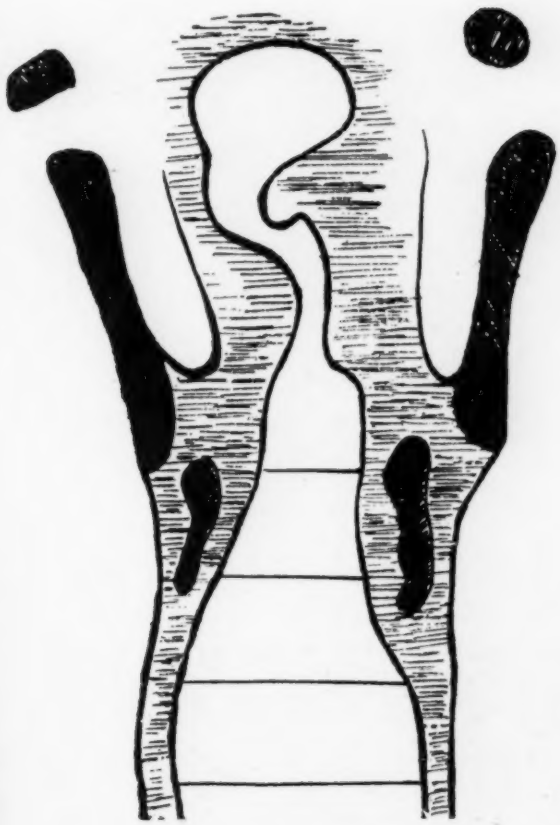


Fig. 14. Drawing of Figure 13.

Fig. 13 (*left*). Frontal tomogram of a case of advanced tumor of the larynx, showing considerable change and deviation of the laryngeal lumen.

ence of an air cavity and may show its communication with the ventricle, even though this is exceptional. The laryngocele may be accompanied by a malignant tumor and simulate an extension of it. In 5 cases which we have observed, one remained after radiotherapeutic treatment of a malignant growth of the subglottis,[4] and another remained after treatment of a tumor of the false cord, giving the impression of a non-sterilization of the tumors.

[4] This is a case of Dr. Coutard's, studied with him at the Chicago Tumor Institute.

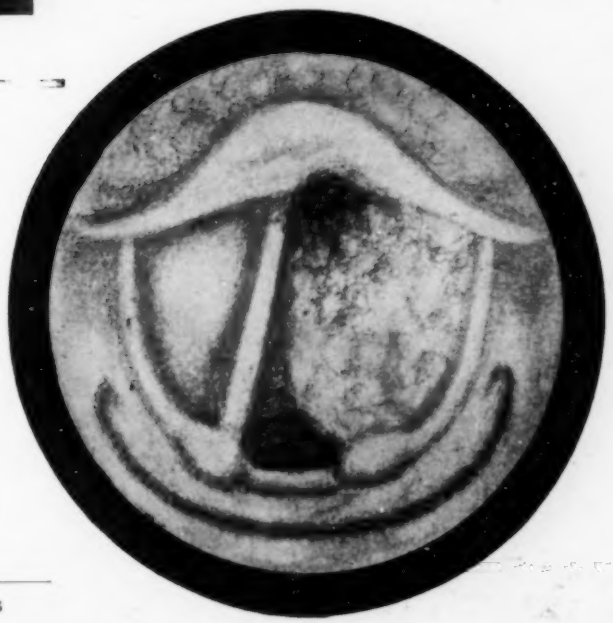


Fig. 15. Tumor of left false cord extending towards end of epiglottis.

Fig. 16. Frontal tomogram of same case shown in Figure 15. Heavy shadow of tumor of left false cord and narrowing of ventricle. The pyriform sinus is also narrowed.

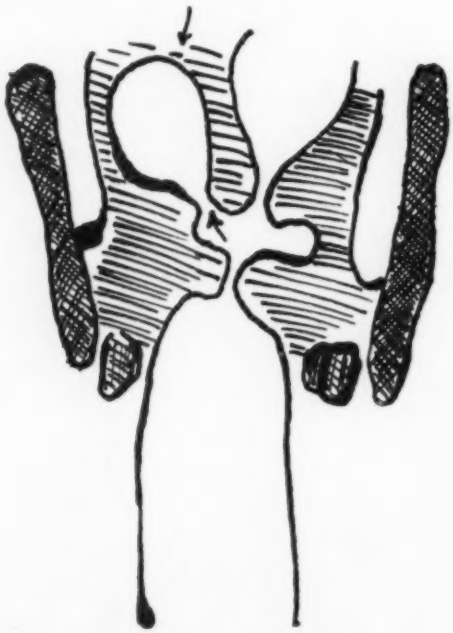


Fig. 18. Drawing of Figure 19.

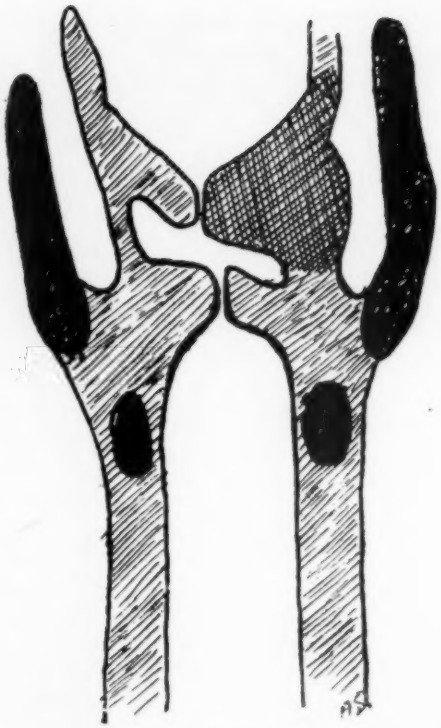


Fig. 17. Drawing of Figure 16.

Fig. 19. Frontal tomogram of a case of laryngocele showing communication with the ventricle.

The interpretation of a tomogram of the larynx is not difficult, but it is necessary to obtain good films to avoid errors of interpretation. The plane of the tomogram must be accurately parallel to the axis of the organ; the films otherwise obtained may give false impressions of the presence of tumors. To be of value, the tomographic examination must be frontal; the films thus taken give a valuable point of comparison of both sides of the larynx.

In the interpretation of tomograms one should follow the symmetry or asymmetry of soft tissues of both sides of the larynx in their relation to the cartilages.

Every case examined by the tomographic method should have had a previous laryngoscopic examination and a profile roentgenogram.

THE VALUE OF NITRITES IN CARDIOSPASM (ACHALASIA OF THE ESOPHAGUS)*

PRELIMINARY REPORT

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THE purpose of this communication is to describe a means of abolishing the esophageal obstruction which occurs in cardiospasm. This can be accomplished in many instances by the use of amyl nitrite or nitroglycerine. The administration of these drugs usually results in partial or total disappearance of the stenosis of the lower end of the esophagus permitting free passage of fluid and food into the stomach. The patient obtains relief from the distressing symptoms associated with the cardiospasm and the roentgenologist is enabled to perform accurate studies of the esophagus and the remainder of the gastrointestinal tract, which he cannot do satisfactorily in the presence of a marked degree of esophageal obstruction and dilatation.

CLINICAL AND ROENTGEN ASPECTS

Cardiospasm is an idiopathic dilatation of the esophagus with a constant or intermittent contraction of the cardiac portion or lower end of the esophagus. No anatomic stenosis is demonstrable and the origin and mechanism of the malady are not clearly understood. It has been thought to be due to a great variety of conditions, among which may be mentioned the following: cicatrices and adhesions in the region of the lower esophagus; endocrine imbalance; neuroses; abnormalities in the diaphragm, liver tunnel or the left lobe of the liver; kinking of the lower esophagus; reflex irritation from cancer of the stomach, peptic ulcer, appendicitis, pulmonary disease, etc.; degenerative changes in the vagus nerve with predominant activity of the sympathetic nervous system. From the large number of etiological factors ascribed to this condition, it is obvious that probably no one of them alone is the true causative factor. Most of the explanations of the cause of cardiospasm are based on the assumption that there is a constant, spasmodic contraction of the esophagus which fails to relax for the ingress of food. However, there is a great mass of clinical and experimental evidence which indicates that no actual spasm exists, or that at least spasm is not the sole factor, in many cases of cardiospasm.

The present view, which is gaining ever-widening acceptance, is that the condition is due to a defective or absent relaxation of a normal tonicity rather than to a spasm. The passage of a bolus of food down the esophagus induces sensory impulses which normally result in a lessening of the tonus of the lower end of the esophagus, permitting passage of the food into the stomach. Failure of this normal mechanism of deglutition results in dysphagia, stenosis of the inferior portion of the esophagus and dilatation above the point of obstruction, the syndrome known as cardiospasm. The condition is, therefore, one of failure of coördination of the muscles of the lower esophagus and the esophageal wall. The term achalasia, which means absence of relaxation at the proper time, is the correct one rather than cardiospasm, which should be discarded and has been retained by us only because it is historically well established and universally used in the literature. In some cases, the entire esophagus dilates markedly and there is actual hypertrophy of its walls, which, nevertheless, fails to overcome the obstruction. Achalasia of the esophagus is believed to be analogous to Hirschsprung's disease, which

* From the Boston City Hospital, Boston, Massachusetts, Department of Roentgenology, P. F. Butler, M. D. Roentgenologist-in-Chief. Read at the Fortieth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 19–22, 1939.

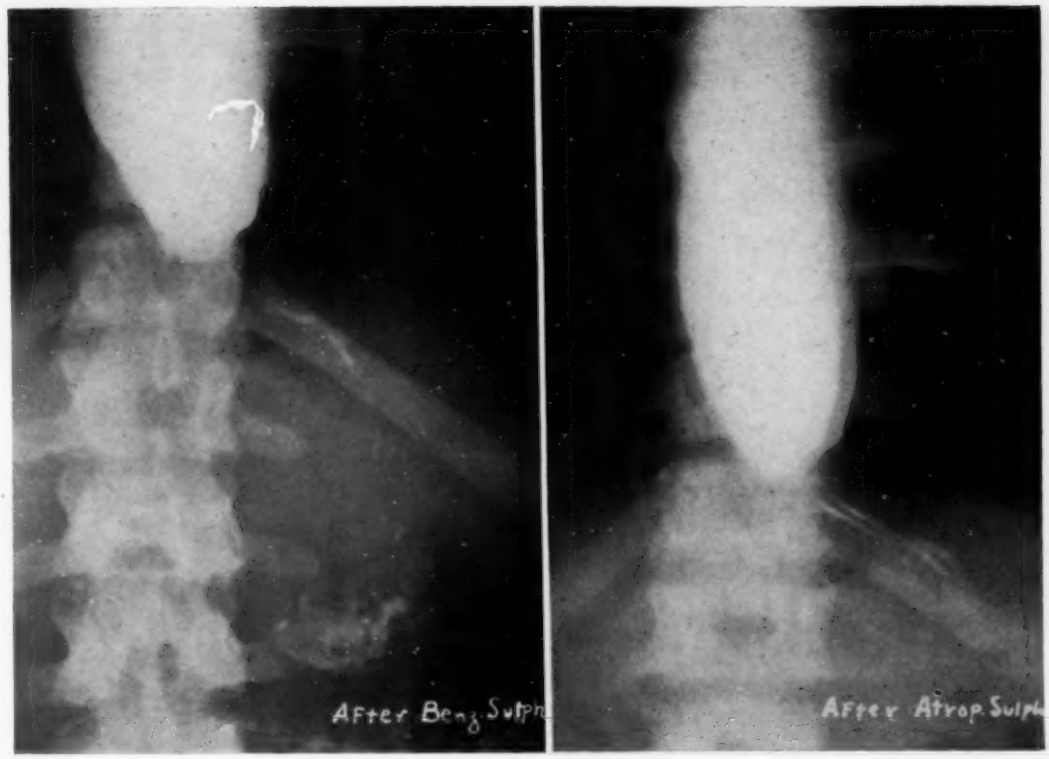

Fig. 1. Cardiospasm, unaffected by benzedrine or atropine. A. B., male, aged twenty-three. Has suffered with severe dysphagia for seven years. Occasional periods of partial relief, but is never completely free of symptoms. Bougies have been passed with slight temporary improvement. Roentgen examination revealed marked dilatation of the esophagus with stenosis of the lower end. After the administration of benzedrine and atropine sulphate, there was no relief of the obstruction.

is due to an imbalance of parasympathetic and sympathetic influences.

Clinically, achalasia of the esophagus is of importance because it is next in frequency to carcinoma in producing the symptoms of esophageal obstruction. Dysphagia, pain in the chest, and regurgitation are the major complaints in patients suffering with this condition. A feeling of weight under the sternum, belching and vomiting of undigested food are common. Progressive loss of weight with severe malnutrition and dehydration may ensue in severe, long-standing cases.

In addition to the suffering caused by the cardiospasm, the obstruction may be a source of much annoyance to the roentgenologist. On roentgen study, the diagnosis rests on the demonstration of a smooth, conical stenosis at or near the cardia with dilatation, often of a very marked degree, above it. Fluid and food particles may result in obscure shadows; also, the esophageal obstruction may interfere with roentgen examination of the stomach, duodenum and intestines as will be discussed in detail below.

DRUGS USED IN OUR STUDIES

A means of abolishing the esophageal stenosis is, therefore, greatly to be desired, not only for the benefit of the patient in relieving his distressing symptoms but also because of the increased ease and accuracy with which roentgen studies may then be carried out. Several drugs were tried without success. Atropine, which has been recommended for many years as an antispasmodic, was found to be totally ineffective even when used in large doses to the limit of physiological tolerance. The bromides and belladonna proved disappoint-

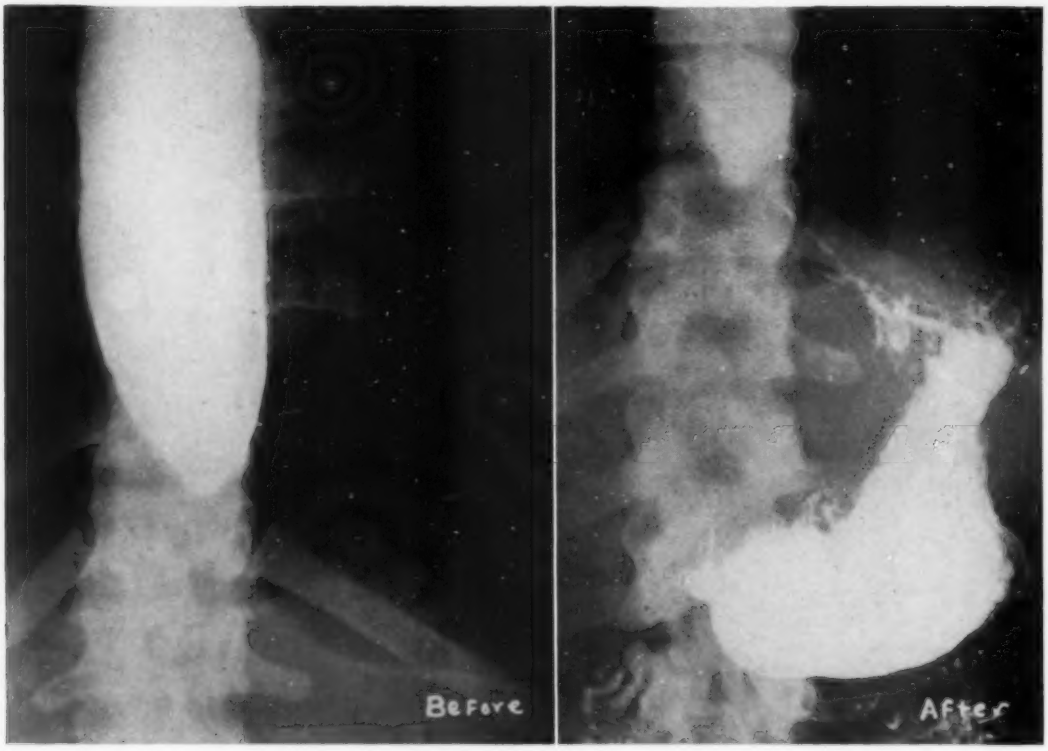

Fig. 2. Cardiospasm, relieved by nitroglycerine. A. B. (same patient as in Fig. 1). "Before" shows the esophageal obstruction and dilatation. After the administration of 1/100 grain of nitroglycerine, the stenosis disappeared and the esophageal contents emptied into the stomach. The patient stated he was aware of the removal of the obstruction.

ing. Benzedrine, which is useful in spasm of the pylorus and intestines[1], produced no relaxation of the lower end of the esophagus in doses up to 30 milligrams (Fig. 1). Various combinations of the above drugs also proved ineffective. Because of the relaxation of the ampulla of Vater[2] and other spasms[3] produced by amyl nitrite, we carried out experiments with this drug. The effects were gratifying. After the inhalation of the vapor, there occurred in most instances an almost immediate disappearance of the stenosis of the lower end of the esophagus with passage of the esophageal contents into the stomach. However, this drug proved not to be the ideal agent for our purpose because it not infrequently caused unpleasant side-reactions. Tablets of sodium nitrite and erythrol tetranitrate were then tried; the effects were slight and very variable. Nitroglycerine was next used and was found to produce satisfactory results in most instances. Doses of 1/100 grain were given to the average patient, very thin or obese persons receiving slightly smaller or larger amounts (Fig. 2). A factor which is of great advantage with nitroglycerine is that this agent is effective by absorption from the floor of the mouth when the tablets are held under the tongue. This is of particular importance in the condition under discussion as the esophageal obstruction results in delayed absorption and consequent ineffectiveness of drugs administered orally in the usual manner. It also avoids the necessity of injection methods, which are objectionable because they may limit the usefulness of the treatment.

METHODS OF STUDY AND EFFECTS OBSERVED

Patients were given the barium mixtures used in the routine examination of the

esophagus. Roentgenoscopic observations were carried out and films taken in the erect position when possible. If cardiospasm was present, the site and degree of obstruction and the extent of the dilatation were noted. Other abnormalities in the esophagus and neighboring organs were carefully sought for. Deep-breathing exercises, reassurance of the patient, and repeated examinations were made to rule out transitory spasm and to establish the constancy of the condition. Then the drug was given. The patients were not told which drug was being used nor what effects were expected. Placebos of saccharum lactis tablets were used at times to rule out purely psychic effects. With amyl nitrite, the pearl was crushed and the patient instructed to take several deep inhalations of the vapor. The nitroglycerine was administered in the form of the soluble hypodermic tablet, 1/100 grain; the tablet was placed in the floor of the mouth and allowed to dissolve under the tongue, the patient being instructed not to swallow for as long as possible.

After the amyl nitrite inhalation, the effect was usually almost immediate. With nitroglycerine, the esophageal obstruction began to disappear in from thirty seconds to four or five minutes. In some instances, the lower end of the esophagus showed definite dilatation with continuous and rapid passage of the esophageal contents into the stomach (Fig. 3); in others, the barium mixture passed downward in a series of spurts with short periods of stenosis intervening between the spurts. In those instances in which the drug was effective, the patients experienced relief and were aware of the removal of the obstruction. The ingestion of more of the opaque meal indicated that the duration of the effect persisted from a few seconds to several minutes, after which time the stenosis reestablished itself as previously. The effect on the heart was very dramatic as observed roentgenoscopically. The cardiac pulsa-

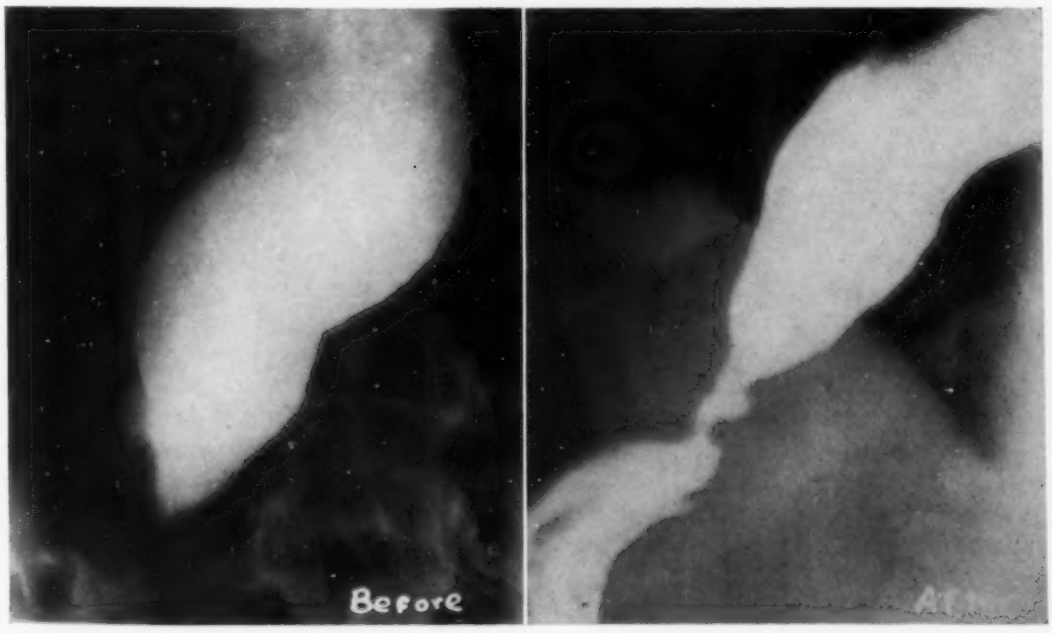

Fig. 3. Cardiospasm. Relief of obstruction by nitroglycerine. P. R., male, aged twenty-four. Acute onset of esophageal obstruction about three years ago. Esophagoscopy showed no organic lesion. Passage of bougies resulted in temporary relief. Roentgen studies (before) showed marked dilatation of the esophagus with stenosis at the cardia. After the administration of 1/100 grain of nitroglycerine, the stenosis disappeared and the esophageal contents passed rapidly into the stomach.

tions became very rapid and of diminished amplitude and the heart shadow appeared to decrease in size. As the effect of the drug wore off, the heart gradually returned to its previous state.

The effects of amyl nitrite were prompt in nearly every case in which we administered this drug. Nitroglycerine was more

THERAPEUTIC EFFECTS OF THE NITRITES

The effects of continued administration of nitroglycerine were observed in 6 cases in order to determine whether the drug had value as a curative agent. Doses of 1/200 grain were given three or four times daily for periods of from three to ten days. On

Fig. 4. Cardiospasm, before and after nitroglycerine. G. O. D., female, aged forty-eight. Gradual onset of dysphagia about three years ago with increasing difficulty during past four months. Roentgen examination prior to giving nitrites revealed marked narrowing of the lower esophagus with almost complete obstruction and moderate dilatation above. After 1/100 grain of nitroglycerine was given, the lower esophagus dilated and the entire esophageal contents flowed into the stomach.

variable and less effective, yet proved more satisfactory for routine use. It has been used in 14 cases with partial or complete abolition of the stenosis in 11 instances. Some of the patients were given the drug on numerous occasions. Roentgenoscopic observations were carried out each time. Increased or repeated doses were used when necessary without serious ill effects. In order to obtain satisfactory roentgenograms showing the effects of the drugs, it is essential that the roentgen machine be equipped with a rapid change-over device so that "spot films" may be exposed rapidly while the patient is under roentgenoscopic control (Fig. 4).

re-examination, the obstruction and dilatation of the esophagus were in every instance found to be present as previously. Administration of another single dose of amyl nitrite or nitroglycerine at the check-up observation after the period of taking the drug again usually resulted in a temporary disappearance of the stenosis. Smaller doses of nitroglycerine, 1/300–1/500 grain, were then administered to a small group of patients every three or four hours throughout the day for several days. The results proved disappointing. Moreover, the patients in some instances tolerated the drug poorly and suffered unpleasant reactions from even these smaller doses.

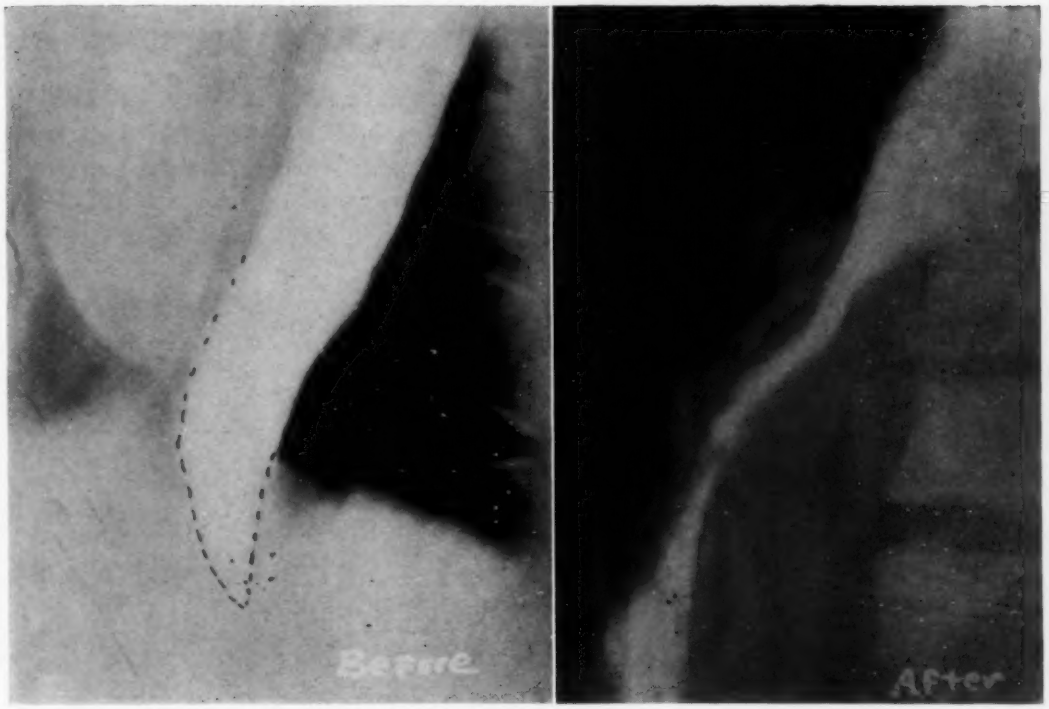

Fig. 5. Cardiospasm relieved by nitrites. E. McK., female, aged thirty-six, married. Acute onset of dysphagia four and one-half years ago. Now states she cannot swallow liquids or solid food, has marked substernal pressure, and vomits frequently. Bouginage has resulted in relief for short periods. The film before giving the drug (retouched) showed complete esophageal obstruction with dilatation of the esophagus. After the inhalation of amyl nitrite, the stenosis disappeared and the opaque mixture flowed into the stomach.

Although the nitrites have proved of no permanent curative value in the true sense of the word, the drugs do nevertheless have a definite though limited application in the treatment of cardiospasm. Patients with severe, chronic achalasia of the esophagus may lose much weight and become severely dehydrated; apprehensiveness with fear of food frequently becomes a factor of serious import; vomiting and regurgitation with choking and severe coughing may cause pulmonary complications. In acute attacks of obstruction, the patient may actually struggle for breath and become cyanotic in attempting to dislodge a bolus of food by violent straining. Temporary relaxation of the stenosis may prove a life-saving procedure in cases of this type, and this relief can frequently be obtained with amyl nitrite or nitroglycerine. Cardiospasm is in many instances associated with neurotic symptoms and a vicious cycle is thereby set up. The breaking of this theoretical cycle by the demonstration that the obstruction may be abolished by these agents may start the patient on the road to recovery in that it removes from his mind the idea that he is afflicted with a hopeless condition from which he can expect no relief. In the treatment of cardiospasm, the passage of bougies may in some instances be facilitated by the use of nitrites just prior to the operation, as the dilatation produced by the drug permits the instrument to pass through the lower esophagus and the danger of perforation or trauma to the esophageal wall is lessened.

VALUE OF ROENTGENOLOGY

To the roentgenologist, the nitrites are

of definite value and serve to increase the ease and accuracy of the roentgen studies of the gastrointestinal tract in cases of cardiospasm. These patients may retain large amounts of fluid and food particles in the esophagus, frequently for long periods of time. Little or none of the opaque mixture required for the roentgen studies may flow into the stomach because of the stenosis, so that satisfactory visualization of the stomach and intestines becomes impossible. It is recognized that carcinoma of the cardia or fundus of the stomach may be associated with esophageal obstruction (Fig. 6); peptic ulcer and other abdominal lesions may similarly produce cardiospasm; and patients with achalasia of the esophagus may present other complaints which make complete roentgen studies of the gastrointestinal tract very desirable. Similarly, disease in the esophagus itself may be overlooked or incorrectly diagnosed in the presence of marked obstruction. Food particles retained in the esophagus produce mottling or filling defects which are easily confused with carcinoma. The fluid in the esophagus causes dilution of the barium mixtures and may obscure ulcers, neoplasms, diverticula and other esophageal lesions. Disease processes in the mediastinum, heart, lungs and dorsal spine may be overlooked or misinterpreted because of

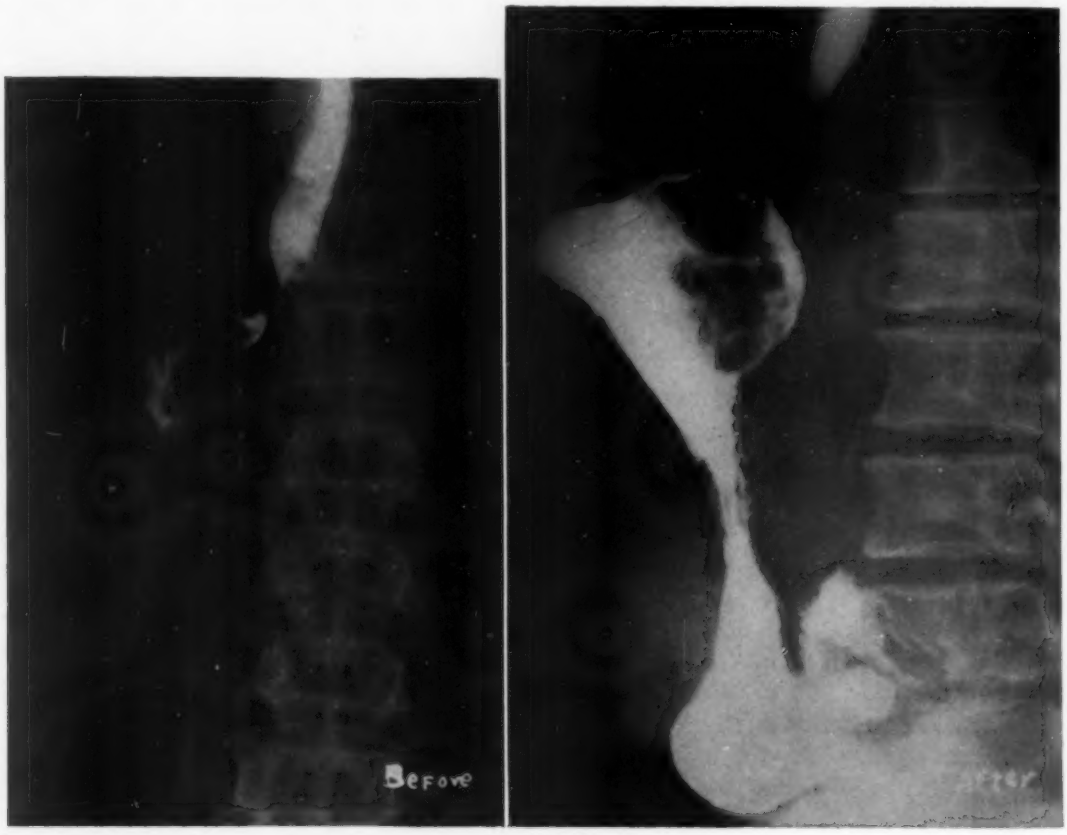

Fig. 6. M. McK., female, aged sixty-nine. Difficulty in swallowing both solid and liquid foods for several weeks. Roentgen studies revealed a stenosis of the lower end of the esophagus. The obstruction was so marked that the patient could take only small amounts of the opaque mixture. Carcinoma of the esophagus was suspected, but satisfactory examination was impossible. After the administration of 1/100 grain of nitroglycerine, the esophageal obstruction disappeared. An extensive neoplasm of the cardia of the stomach without involvement of the lower end of the esophagus was demonstrated.

the confusion resulting from the overlying shadows of the dilated, fluid-filled esophagus. Attempts to eliminate these difficulties have previously required esophageal lavage or dilatation by bougies. It is simpler, safer and more satisfactory from the point of view of both patient and physician to avoid these procedures by the comparatively simple expedient of administering amyl nitrite or nitroglycerine.

SIDE-EFFECTS

The nitrites are very prone to cause unpleasant reactions. With amyl nitrite, the side-effects may be marked and definitely limit the usefulness of the drug. The pungent odor is very objectionable to many patients. Giddiness and fainting with complete loss of consciousness occur frequently. If the patient is erect, which is the preferable position in the roentgen study of the esophagus, he is very apt to faint and fall to the floor. This drug is therefore best used with the patient recumbent, careful watch being kept for reactions. Patients with severe coronary disease or angina should be given amyl nitrite with caution. In no instance were there any serious after-effects in our cases, and we feel the drug may safely be used within the limits mentioned above.

Nitroglycerine also produced untoward reactions; however, they were milder and less troublesome. Flushing and perspiration were the most common ill effects. Nausea and vomiting were apt to occur. Throbbing and pounding headaches, giddiness and vertigo were present in many patients. Fainting occurred rarely. In none of the patients were these reactions serious and many persons suffered no ill effects from single doses. A striking fact is the extremely wide variation in tolerance of different individuals.

SUMMARY AND CONCLUSIONS

Cardiospasm is an idiopathic stenosis of the lower portion of the esophagus with marked dilatation above the point of obstruction.

The condition is believed to be due to a defective relaxation of the normal tonicity rather than a spasm and should more properly be termed achalasia of the esophagus.

There has previously been no satisfactory method of abolishing the esophageal obstruction except by mechanical dilatation.

The administration of amyl nitrite or nitroglycerine produces a disappearance of the stenosis of the esophagus in many cases of cardiospasm, permitting the passage of fluid and food into the stomach.

The abolition of the obstruction in those cases in which the drug is effective gives the patient relief from his distressing symptoms; it permits of accurate roentgen visualization of the esophagus and the remainder of the gastrointestinal tract; the passage of dilators may be facilitated and the dangers of traumatism or perforation during instrumentation lessened.

The effect of the drugs is of short duration; nevertheless these agents appear to have a definite though limited application in the treatment of cardiospasm.

We wish to express our appreciation to Dr. P. F. Butler, Roentgenologist-in-Chief at the Boston City Hospital, Boston, for his cooperation and assistance in the preparation of this paper.

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DISCUSSION

Dr. Richard B. Capps, Chicago. Very little has been written regarding the use of nitrites in cardiospasm, and I think that Drs. Ritvo and McDonald have shown that they have a very definite place in this condition. It is well known that atropine and related compounds are ineffective in those types of cardiospasm which we may call "achalasia." Hearst, Cameron, Wright

and others, have been fortunate enough to have had the opportunity of examining histologically a number of these cases and they have been able to demonstrate the anatomic reason for this fact. They have found in practically all of such cases a destructive lesion involving Auerbach's plexus of nerves. Since the vagus nerve acts through this plexus on the smooth muscle of the esophagus, atropine would not be expected to have any effect. Furthermore, the normal relaxation of the cardia at the end of swallowing would not be expected to occur. Nitrites, on the other hand, since they act directly on the smooth muscle, would still be effective.

These cases Hearst called "achalasia of the cardia," simply meaning failure to relax. These are the cases that show the most pronounced symptoms and findings both clinically and roentgenologically, namely, marked dilatation of the esophagus and very marked dysphagia. Clinically, however, there is a large group of other cases that are termed cardiospasm where dysphagia is not such an important finding, where pain is perhaps the presenting symptom. Such patients frequently do not show any abnormalities on roentgen examination and atropine is usually a successful therapeutic agent.

I should like to reaffirm Dr. McDonald's remarks concerning the bad effects of nitrites. I do not believe they will prove very satisfactory as regular treatment for cardiospasm. In the first place, as he stated, they have a very transient effect. There is no permanent benefit. The discomfort associated with them is frequently too great to make them satisfactory and, finally, in a great many cases we have other more satisfactory forms of treatment. As a diagnostic procedure under the fluoroscope they undoubtedly are extremely valuable.

I should like to reaffirm one other statement that syncope not infrequently occurs in certain individuals following the use of nitrites. Although this is not a serious situation in younger persons, there are a great many older people where it might result rather seriously and I think this should be taken into consideration. Of course, if the patient is not in an erect position, syncope is not so likely to occur and immediately putting him in the prone position will usually bring relief.

Vol. 43, No. 4

CHARCOT'S ARTHROPATHY OF BOTH ANKLES*

CASE REPORT

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TABETIC arthropathy has been known since Mitchell called attention to it in 1831. It was not until after Charcot's original description in 1868 of the destructive joint lesion which has come to bear his name that the condition began to receive wide recognition. Since then numerous case reports as well as detailed discussions of all phases of the subject have been published. Just to cite a few pertinent to the present report:

Charcot himself in 1873 noted the occurrence of spontaneous fractures in tabes; Steindler, in a series of 64 cases of neuropathic joints, found 11 spontaneous fractures including one of the astragalus; Stewart, in his recent article, included a case of bilateral involvement of the astragalus.

It is merely intended to submit a brief case history with illustrations which should be of interest because of the unusual opportunity afforded to follow the progress of the condition from its inception to the fully developed state.

CASE REPORT

H. G., white male, aged forty-six, was admitted to the Veterans' Administration Facility, North Chicago, Illinois, on March 26, 1936. He had been under observation at various Veterans' Administration Facilities since 1932 when he was treated for an injury of the right great toe. In 1910 he had contracted gonorrhea and a primary genital chancre. On March 29, 1932, the blood Wassermann was 3+ and the Kahn 2+. He was accordingly given a course of antiluetic therapy consisting of bismuth and arsphenamine. On July 14, 1932, blood Wassermann was negative and the Kahn 1+, but a neurological examination revealed fixed pupils, sluggish knee jerks, and absent ankle jerks. The diagnosis of early tabes dorsalis was made. (Spinal puncture was refused.) Another course of antiluetic treatment similar to the first was administered.

Between June, 1933, and July, 1934, patient worked in a C.C.C. camp. Then he began to have shooting pains in the legs and swelling and inflammation of the feet in the warm weather. In August, 1934, he was confined to bed for about four weeks with "rheumatism." Finally, on November 15, 1934, he was again hospitalized by the Veterans' Administration. At this time his ankles were enlarged and somewhat tender, but motion was full. There was a severe degree of pes planus, bilaterally. A roentgenogram taken November 16, 1934, revealed no evidence of bony changes of the feet or ankles, but the medial aspect of the right ankle was rather prominent (Fig. 1). Blood, spinal fluid, and Wassermann were negative. The Lange colloidal gold test was not satisfactory. There were three cells per cubic millimeter of spinal fluid. He was given a full three months' course of mercury rubs, bismuth, and tryparsamide.

On April 23, 1935, he was sent to the Soldiers' Home for domiciliary care and he remained there until September 14, 1935, receiving another course of bismuth and tryparsamide during this period.

On September 20, 1935, he was again hospitalized. He complained of pain in the feet on standing and walking. A marked prominence of the inner aspect of both ankles, especially the right, was noted. A roentgenogram taken September 27, 1935, showed separation of the posterior process of the left astragalus and destructive changes of the posterior process of the right astragalus and irregularity of the right navicular bone (Fig. 2). By December 31, 1935, the condition had become more pronounced so that on roentgen examination a medial dislocation of the right astragalus was seen (Fig. 3). There was marked relaxation of all the ligaments. At this time a diagnosis of early bilateral Charcot's disease of the ankles was made. He was again given antiluetic therapy consisting

* Published with permission of the Medical Director, Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the writer.

Fig. 1. November 16, 1934. *A*, dorsoplantar and *B*, lateral roentgenograms showing no demonstrable bone changes.

Fig. 2. September 27, 1935. *A*, dorsoplantar roentgenogram showing beginning medial displacement of right astragalus and area of rarefaction of left. *B*, lateral view showing destructive changes in each astragalus and irregularity of right navicular.

of a complete course of bismuth and trypars-amide, and part of another course.

He developed mental symptoms so that the diagnosis of taboparesis was made and on March 26, 1936 he was transferred to the hospital at North Chicago, Illinois. On admission

Fig. 3 (*right*). December 31, 1931. Displacement and rarefaction are more marked.

Fig. 4 (*below*). March 31, 1936. *A*, dorsoplantar roentgenogram showing spontaneous (pathologic) fracture of right astragalus, with dislocation. *B*, lateral view showing involvement of posterior articular surface of right calcaneus as well as right astragalus.

Fig. 5. Photograph showing deformity at present.

he complained only of his feet being tired when he stood on them any length of time. He was partly disoriented, somewhat euphoric, and lacked insight. Essential neurological findings were fixed pupils, sluggish knee jerks, and absent ankle jerks. The Romberg sign was only suggestive. Vibratory sensibility and deep pain were decreased over both ankles, more so on the right. However, muscle and position sense as well as pain and temperature were retained. There was marked deformity of the right ankle, as is shown in Figure 6, but no tenderness. Roentgenogram taken March 26, 1936, revealed a fracture dislocation of the right astragalus, an area of rarefaction in the left astragalus, and early destructive changes in the right calcaneus, in addition to the changes previously noted. Spinal fluid and blood Wassermann were negative. Lange colloidal gold test was 0012333210. He was given intensive antiluetic treatment which included three full courses of bismuth and tryparsamide and full doses of potassium iodide, as well as malarial therapy.

There has been little change in the condition of the ankles other than an increase in density of the right astragalus. This is demonstrated by the last roentgenograms taken on March 5 and 8, 1938. Various orthopedic appliances have been used and at present the patient still tires if he is on his feet too long, but he is fairly comfortable with the use of an appliance which protects the medial aspect of the right ankle. Surgical measures have not been considered advisable by the orthopedic consultants. His mental condition has improved somewhat so that the principal manifestation is now a somewhat defective memory.

DISCUSSION

The following points should be noted:

(1) Tabes was recognized clinically as early as 1932. In July, 1934, patient began to complain of his feet and legs, but at no

Fig. 6. Latest roentgenograms. *A*, March 8, 1938, and *B*, March 5, 1938, demonstrating increased density of right astragalus.

time was there any history of acute severe symptoms referable to the right ankle.

(2) Patient received a number of courses of antiluetic therapy before any bone lesions were demonstrable on the roentgenogram; yet the destructive bone changes developed and progressed rapidly so that in less than a year and a half after a negative roentgen finding, there was a marked deformity of the right ankle. The experience of other observers has been more favorable, however. For example, Alajouanine was able to secure improvement after involvement of the cuboid and navicular bones was already demonstrable by roentgen examination.

(3) Unfortunately, no spinal fluid examination was available before antiluetic therapy had been given. However, one spinal fluid examination in 1934 and two in 1936 gave a negative Wassermann reaction.

Steindler, quoting a number of other observers, states that spontaneous fracture may be the first sign not only of arthropathy but also of tabes itself and that an interval of two to three years between the spontaneous fracture and the initial tabetic symptoms is not uncommon. In this case, the clinical findings of tabes were present about four years before the fracture was demonstrated.

While the onset of the Charcot's joint is frequently sudden, as described by Stewart and others, yet many cases of insidious onset have been reported, as in the present case.

I wish to acknowledge my appreciation to the hospital authorities for the aid extended in securing material and also to thank Mr. Robert Heth and Mr. Ray Dornfeld who prepared the photographs and prints.

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TRAUMATIC PNEUMOCRANIUM

A REPORT OF TWO CASES*

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PITTSBURGH, PENNSYLVANIA

ACCIDENTAL introduction of air into the cranial cavity was first described by Chiari in 1884. In the American literature, a comprehensive review of this subject was presented by Dandy[1] in 1926. Smith and Malcolmson[2] stated that 43

FIG. 1. Case 1. Lateral view with roentgen beam horizontal. Made immediately after death. The large collection of air beneath the frontal bone is well seen. The anterior cerebrum is compressed. There is a fluid line passing through the sella turcica. This was the condition found on the portable examination the day after admission.

cases had been described up to 1931. Madigan[3] and Taft[4] each contributed a case report subsequently.

This communication presents 2 additional cases with this rare condition and emphasizes a point in the technique of its roentgenographic demonstration.

CASE 1. J. A., white male, aged fifty-five, was brought to the hospital by police on November 1, 1938. He was stuporous and had been drinking. The only history available was that he had fallen down a flight of stairs a short time before admission. On examination, his pupils were found contracted, and the ocular movements uncoördinated. There was a serosanguineous discharge from the right ear. Blood pressure 130/90. No other neurological findings.

Portable roentgen examination the next day showed evidence of an extensive fracture through the base of the skull, probably involving the nasopharynx. There was a large collection of air within the skull which shifted with change in position of the head. This was considered a pneumocranium with the air in the subdural space.

The patient never regained consciousness. Temperature and pulse steadily climbed, and he died on the third day after admission.

An autopsy was performed by the coroner. An extensive fracture of the base of the skull was found. One part of the fracture ran upward

FIG. 2. Case 1. Lateral view with roentgen beam vertical. Made immediately after death. Although the pneumocranium is still well seen, the fluid line has disappeared. It is possible that small collections of subdural air would fail to show in this projection.

* From the Department of Roentgenology, Allegheny General Hospital, Pittsburgh, Pa.

and backward from the foramen magnum to involve the occipital bone. The other ran upward and forward from the foramen magnum involving all the structures of the base and traversing the sphenoid sinus and the sella turcica to end in the posterior nasopharynx.

Case II.* C. W., a white male, aged fifty-eight, shot himself through the right temple on October 13, 1938. He was found semi-conscious in his room several days later and was brought to the St. Francis Hospital on October 21. On examination, he was stuporous but could be aroused. He was blind in both eyes with evident intraocular hemorrhage in the right. No other neurological signs.

Roentgen examination the same day showed a bullet just inside the left zygoma with a train of lead dust extending back of the orbits to the hole of entry in the right temporal bone. In the posteroanterior projection, there was a small collection of air in the midline in the region of the falx which was interpreted as a subdural pneumocranium.

On October 22 the patient became more alert. Relatives signed him out of the hospital, and he disappeared.

* Presented through the courtesy of Dr. Leslie H. Osmond, Radiologist at St. Francis Hospital, Pittsburgh, Pa.

Fig. 4. Case II. Posteroanterior view made with the patient prone. Note the collection of air adjacent to the falx in the midline. The bullet and its path are well shown. Lateral views of the head did not demonstrate the pneumocranium.

Fig. 3. Case I. Posteroanterior view with roentgen beam vertical. Made immediately after death. The subdural air has shifted with change in position of the head and now outlines the cerebral hemispheres. A part of the fracture lines is seen near the midline.

The mechanism by which air is trapped within the skull in traumatic pneumocranium has been well described by others.[1,2] The mortality in untreated cases is 50 per cent. In the great number of head injuries associated with automobile accidents, this condition must occur more often than hitherto recognized. It should be suspected in all skull fractures in which a serosanguineous discharge occurs from nose or ears; or in which the fracture extends into the sinuses.

In routine films of the head with the roentgen beam vertically placed, a small amount of subdural air evenly distributed over the cortex might be overlooked. Therefore, when pneumocranium is suspected, it

is necessary to make additional films in the posteroanterior and lateral projections with the roentgen beam horizontal.

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Vol. 43, No. 4

THE GASTROINTESTINAL RESPONSE OF AVERAGE, HEALTHY CHILDREN TO TEST MEALS OF BARIUM IN MILK, CREAM, MEAT AND CARBOHYDRATE MEDIA*

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IN A ROENTGENOLOGICAL study of the behavior of the pyloric sphincter it was shown that acid concentration is not the principal factor controlling the opening and closure of the pyloric sphincter in man nor is the initiation of gastric emptying affected by the difference in consistency (viscosity) of various foodstuffs.[15] More recently, quantitative studies have demonstrated that although hydrochloric acid is an efficient stimulus for the enterogastric reflex, the quantity excreted into the stomach is generally so diluted that after passing through the pylorus there is seldom an effective concentration in the intestine.[7] On the other hand, it has been demonstrated that gastric tone and the force of gastric peristalsis may be changed by different stimuli applied in adequate strength to the small or large intestine. Among the conditions within the intestine that affect gastric motor activity are mechanical distention, chemical irritation, the action of hypertonic or hypotonic solutions, and the presence of products of protein and starch digestion. It had been proved that fat[10,12] and carbohydrate[23] inhibit gastric secretion and motility through a humoral mechanism whose active principle has been given the name of enterogastrone. Subsequently, experiments on the extract of the duodenal mucosa containing enterogastrone suggest that the e may be *two* active principles, one whi h inhibits secretion and another which inhibits motility.[10] This mechanism, which affects secretion and motility, whether it be of humoral or nervous nature, or both, no doubt exerts a strong influence in providing suitable conditions for digestion of the various foodstuffs.

Fat, presumably, modifies gastrointestinal activity through an inhibitory effect on gastric secretion and motility, thus rendering the duodenal contents neutral or only slightly acid.[28] Carbohydrates entering the normal, empty stomach inhibit hunger contractions, and the same phenomenon occurs in the denervated stomach as the result of a humoral factor (not carbohydrate *per se*) produced by the presence of carbohydrate in the upper intestine.[22] The inhibition persists until the onset of digestive contractions, an interval which is short following ingestion of usual amounts of carbohydrate but which may lengthen to several hours when concentrated solutions are present. Apparently this restriction is physiologically significant in controlling the rate at which carbohydrate may enter the duodenum;[13] in any event, there is an accumulation of evidence that there is a genuine dissociation between the secretory and motor activities of the stomach.[10,19] One of the popular dietary fads today forbids the consumption of carbohydrate and proteins at the same meal, the underlying theory based upon the fact that proteins require a high gastric acidity for initial digestion while carbohydrates need an alkaline medium. It has been shown that carbohydrate and protein combined in one meal do not interfere with gastric secretion, and furthermore, that carbohydrate digestion is prolonged and encouraged by mixtures with protein.[26]

The motility and secretion of the various

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segments of the alimentary canal are recognized as the prime factors influencing, and influenced by, other processes concerned in the utilization and excretion of foods. Many experimental procedures have been instituted in an effort to determine accurately some of these relationships. The conditions of experiment, in many instances, have prevented any interpretation of the results as those of the natural response. It has been demonstrated that many factors are interrelated in the determination of the response of the alimentary canal: the method of measurement;[29,33] the size of the meal ingested;[31,32] its temperature, consistency and content;[29] the nutritional state of the individual; and, the emotional and environmental conditions to which the individual is subject at the time.[4] The difficulty in obtaining estimations of the gastrointestinal response of individuals within the range of "normal" has been the inability to obtain measurements upon trained and standardized subjects under adequately controlled conditions which do not interfere with natural response. The difficulties inherent in studies of animals or adults are greatly magnified in attempts toward determining the gastrointestinal responses of children, for consideration must be given to the possible effects of their individual physiological time of progress in growth and possible influences of the growth process itself.

Following the completion of a rigidly controlled metabolic study of average, healthy children over eight consecutive months, roentgenological studies were made of: their gastrointestinal motility and the variations which may be expected from time to time;[17] the effect of carmine upon their gastrointestinal response;[16] and the variation in response due to different types of milks.[25] During the metabolic study of chemical growth, the gastrointestinal motility of the subjects was studied by means of carmine markers given every fifth morning to demarcate the fecal unit of each balance period, and by the records of the frequency and wet and dry weights of their defecations over 225 consecutive days.[20] The gastrointestinal response of the same subjects to five different types of test meals is reported in this paper.

The subjects of the studies were carefully chosen as representative of average, healthy children from their medical histories and the results of thorough clinical and laboratory examinations.* The children were within normal limits in bone and structural development and mentality.† Throughout the study the children, between four and one-half and eight years of age, were subject to the same highly standardized conditions of adequate diet, routine and environment favorable to growth and development which had been maintained during the metabolic investigations.‡

EXPERIMENTAL PROCEDURE

Series of roentgenograms were made showing the gastrointestinal tracts of the subjects at frequent intervals following ingestion of test meals composed of barium in five different types of media. An interval of at least one week elapsed between any two series with the same child. The liquid meals were given at body temperature, the solid one at room temperature. The liquid meals all consisted of 2 ounces of barium sulfate in 4 ounces of medium. Water was used as one carrier, providing an inert meal. Meals of different fat content were procured by using 4 ounces of milk (3.5 per cent fat) and 4 ounces of cream (20 per cent fat) as media for the barium. A carbohydrate meal was formed with the barium in 3 ounces of water and 1 ounce of corn syrup (approximately 30 per cent glucose, 61 per cent carbohydrate). A protein test meal was composed of 40 grams of barium sulfate mixed with 100 grams of raw ground lean meat, baked twenty to thirty minutes and ingested with 200 cc. of water. Based on the total weights of the meals at the

* Marsh W. Poole, M.D., pediatrician for the Methodist Children's Village, made frequent examinations of the children.

† The late T. Wingate Todd, M.D., and C. C. Francis, M. D., Western Reserve University, Cleveland, evaluated the roentgenograms of the subjects and estimated their skeletal ages. The Children's Center, Child Guidance Division of the Children's Fund of Michigan, made the psychological tests.

‡ The results of the integrated program of investigation of the chemical growth of average, healthy children forms the material for a monograph upon that subject, now being prepared.

times they were ingested, the milk meal had a concentration of 2.33 per cent fat; the cream meal, 13.33 per cent fat; one meal had a concentration of 10 per cent carbohydrate; and the meat meal was approximately 3.5 per cent fat and 7 per cent protein.*

All meals were ingested in a few minutes except the meat loaf, for which one-half hour was allowed. The children's routine was interfered with as little as possible. No laxatives were given or any alteration made in the diets preceding the studies. The barium meals were given in the morning and were the only food ingested between the evening meal preceding and the completion of the first day's roentgenograms.

After ingestion of the first meal given (water), a roentgenoscopic examination was made (L.R.) to eliminate the possibility of any abnormality in the chest, in the movement of either leaf of the diaphragm, or in the rate or rhythm of the heart. The first exposure in each series was made within twelve minutes after the meal was ingested and additional films were exposed at thirty minute or hourly intervals up to about five hours, in the case of the faster meals, and seven hours in the cases of the slower ones. Throughout the period of observation at frequent intervals (four to eight hours) the subjects were allowed the freedom of a room in which they played; however, they were under strict surveillance at all times to preclude ingestion of food or water. Additional roentgenograms were procured twenty-four, forty-eight, and in a few instances seventy-two hours, approximately, after ingestion of the meals.

The roentgen examinations were made with the subjects in prone position with the target 31 inches from the film and centered on the first to second lumbar vertebra; exposure was $\frac{1}{5}$ sec. at 92 kv. (peak) and 50 ma. with Potter-Bucky diaphragm. Patterson par-speed screens were used with the smaller children and speed screens with the larger ones. To eliminate some of the obvious difficulties in comparison or evaluation, each roentgenogram was photographed and reduced to a $1\frac{1}{2}$ by $2\frac{1}{2}$ inch reproduction. Each series of prints was then mounted upon a cardboard strip, making direct and comparative estimations possible.

* During cooking the water lost was approximately 50 grams. The resulting meat loaf contained, roughly, 10 grams of fat and 20 grams of protein, providing concentrations in the total 290 grams of the meal of approximately 3.5 per cent fat and 7 per cent protein.

RESULTS

Of the roentgenograms made in this study of the variations in the motility of the different segments of the gastrointestinal tract of children, the reproductions of the exposures illustrative of the five barium meals (water, glucose, milk, cream and meat) in 4 subjects at comparative time intervals are presented in Figures 1–7. All of the series of roentgenograms show the same wide range of individual variation which characterized the subjects during the previous study over eight continuous months and the physiological pattern described in the preceding report.[17] Variations in the size, shape, and position of the stomachs of all subjects filled with the same amount of meal are apparent but no anomalies are portrayed.

Emptying Time of the Stomach. In Table 1 are given the physical data and the gastric emptying times for the different individuals in the 33 series of observations made. The inert water meal emptied from the stomachs (average 1.9 hours) appreciably faster than any of the other meals. The average emptying times for the milk and glucose meals were 3.1 and 3.3 hours, respectively, and for the meat and cream meals 5.0 and 4.8 hours, respectively. It is evident that the type of vehicle or conveyer of the barium has a specific motor effect upon the egression of the meal through the pylorus, findings which substantiate those of Johnston and Ravdin[13] and Gershon-Cohen and Shay.[8]

The products of carbohydrate,[23] fat[13,22] and protein[9,31] digestion are known to have a physiological significance in controlling the rate at which these substances enter the duodenum, whether through a humoral or nervous action or both on the pyloric reflex mechanism by way of the small intestine. In the present series of observations the water meal began to leave the stomach immediately following its ingestion and within ten minutes a considerable amount of barium mixture had entered the jejunal loops (Fig. 1). With the water-

barium meal the stomach exhibited a normal two-wave type of peristalsis. There was no pylorospasm and no abnormality in the orderly egress of the meal, the stomachs completely emptying their barium content within 2.8 hours (average 1.9 hours), and the barium distributing throughout the small gut as shown in detail in the accompanying illustrations. On the contrary, the carbohydrate-barium meal increase in volume of gastric contents and a decrease in their concentration. Ravdin, Johnston and Morrison[24] found that though 215 cc. of glucose solution was the maximum amount of fluid introduced into the stomach, more than 500 cc. were removed at the end of an hour, the additional water having been drawn into the stomach as a diluent for the sugar solution. Concentrations of glucose varying from 3.5 to 50.0

Table I

PHYSICAL DATA AND GASTRIC EMPTYING TIMES WITH DIFFERENT TYPE FOODS

Subject	Sex	Age	Recumbent Length	Weight	Physical Type*	Gastric Emptying Times†					Average Number Defecations During 8 Months' Metabolic Study
						Water	Milk	Meat	Cream	Carbohydrate	
		mo.	cm.	kg.		hr.	hr.	hr.	hr.	hr.	per day
D.P.	M	117	143.5	34.05	0.0226	1.0	3.0	3.5	2.5	3.0	1.2
W.P.	M	113	126.2	27.78	0.0240	2.0	3.0	4.5	5.5	3.0	1.6
H.H.	M	102	129.7	26.56	0.0230	2.0	1.5	—	—	—	1.6
P.W.	F	98	127.8	25.51	0.0231	1.5	—	7.0	—	—	1.0
F.C.	M	96	128.0	26.79	0.0234	1.8	4.0	3.0	6.5	3.0	1.4
R.S.	M	88	123.7	22.36	0.0228	2.8	2.5	7.0	4.5	4.0	2.4
B.F.	F	86	117.6	21.68	0.0237	1.5	—	—	—	3.5	1.6
B.M.	F	81	114.7	19.07	0.0234	2.5	4.5	6.0	—	—	1.7
J.H.	M	74	117.4	21.91	0.0238	1.3	3.0	5.0	—	3.0	1.8
Mean						1.9	3.1	5.0	4.8	3.3	1.6

* (Cube root weight) divided by recumbent length.
† Times given are from completion of ingestion of test meals.

(10 per cent) retarded the gastric motility to a maximum of four hours (average 3.3 hours). These results are in agreement with recent experimental work on gastric physiology in man[8,13,19,24] involving the influence of osmotic pressure change produced by sugar solutions on pyloric action and suggest that osmotic pressure above or below isotonicity definitely influences pyloric action and gastric evacuation, and the greater the hypertonicity of the test meal, the slower the gastric emptying.

It has been found that the body, which is organized for physiological homeostasis,[2] always attempts to bring the ingested fluid to the isotonic state; consequently, when a hypertonic solution is introduced into the stomach there follows a rapid mg. per 100 cc. were given and after an hour the concentrations of glucose in the small intestine only varied from 2.6 to 5.3 mg. per 100 cc., irrespective of concentration given.

Gershon-Cohen and Shay[8] conclude that "the pyloric action was motivated locally through duodenal stimulation by chemical action, and that this same mechanism is influenced by physical stimuli as represented by changes in osmotic pressure away from isotonicity. Gastric emptying time alone cannot be used as an index of pyloric function when considering osmotic tension of agents given by mouth because of the migration of fluid which takes place through the stomach wall when the test meals are not isotonic."

Consideration of the physiological homeostatic effect of the stomach in rendering an ingested hypertonic fluid isotonic makes very valuable a comparison of the changes in the volume of the stomach contents of the same individual when inert and hypertonic substances are used as conveyers of the barium. Although it is recognized that planimeter measurements of the roentgenograms, representing the square centimeter area of the maximum longitudinal section of the stomach containing these different barium meals, has its limitations so far as exactness is concerned (the third dimension cannot be obtained[30]) yet qualitative information significant to the roentgenologist can be secured (Table II). From the measurements of the barium shadows of the stomachs when filled with equal quantities of the inert water-barium mixture and the slightly hypertonic carbohydrate-barium meal it is obvious that there are variations in the stomach size of the different subjects and that even by the time the first film could be taken, the carbohydrate meal caused a significant increase in size of the stomachs.

The increases in the average differences between the size of the stomachs with the water and carbohydrate meals after forty and seventy-five minutes (Table II) emphasize the length of time devoted to rapid dilution of the sugar mixture. Inspection of Figures 2 and 3 accentuates the fact that while little progress is made in the emptying of the carbohydrate mixture from the stomach, a quantity of barium carrier, equal or greater than with water meal has been emitted into the small intestine by the end of seventy-five minutes. It would seem that the intestinal response to the carbohydrate meal involves not only the original 6 ounce meal but also an increase of several times that volume.

If the sizes of the stomachs (Table II) are stated in terms of per cent of their measurement twelve minutes after the water meal (assuming the size twelve minutes after ingestion of the water meal to be 100 per cent) the average increase in size due to substitution of the sugar for water is 41 per cent. At the three intervals (Table II) the average sizes of the stomachs were: with the water meal after twelve minutes, 100 per cent; after forty minutes, 72 per cent; and after seventy-five minutes, 63 per cent; with the glucose meal after twelve minutes, 128 per cent; after forty minutes, 122 per cent; and after seventy-five minutes, 117 per cent. While the size of the stomach increased rapidly and then decreased much more slowly with the sugar meal, it remained larger after seventy-five minutes than with the water meal after twelve minutes.

These results verify the findings that a hypertonic solution does cause an increase

Table II

Influence of hypertonic carbohydrate solution* upon the size of the barium shadow of the stomach as measured by the planimeter†

Child	Barium Medium Used	Surface Area of the Stomach after Ingestion of Barium Meal		
		12 min.	40 min.	75 min.
		(sq. cm.)		
D.P.	Water	60	‡	‡
	Carbohydrate	85	‡	‡
W.P.	Water	66	52	42
	Carbohydrate	83	86	82
F.C.	Water	76	53	48
	Carbohydrate	99	92	87
R.S.	Water	85	60	52
	Carbohydrate	107	104	97
B.F.	Water	83	57	‡
	Carbohydrate	94	96	‡
J.H.	Water	65	‡	‡
	Carbohydrate	84	‡	‡
	Average difference	20	39	41

* Corn syrup used in the carbohydrate-barium mixture produced a concentration of 10 per cent carbohydrate.

† The planimeter used was a disc planimeter made by G. Coradi, Zurich.

‡ Complete stomach not shown on both films precluded measurement.

in the volume of the gastric contents.[24] Moreover, they explain the satiety and sense of fullness followed by a cessation of hunger contraction and a submerging of appetite which follow the consumption of candy or sweets at any time.

A study of the protocols of the milk-barium meal shows that there was an initial delay in the passage of this meal through the pylorus into the small gut, producing an average gastric emptying time (Table 1) of 3.1 hours in contrast to 1.9 hours with the water barium meal. Twelve minutes following ingestion of the milk meal the stomachs of 8 subjects still retained all of the milk-barium mixture. Moreover, the first films exposed (Fig. 1) show the presence of only one peristaltic wave in the stomachs. The second films (Fig. 2), exposed thirty minutes later, show an orderly two-wave type of peristalsis in the stomachs and some of the barium mixture in the distal jejunal loops. The subsequent films exposed (Figs. 3–7) show an orderly emptying of the gastric content and the normal passage through the small gut, the small intestine pattern being somewhat at variance with that shown in the barium-water meal series. These results are in agreement with those of Gershon-Cohen and Shay[9] who found that during the early stages of milk digestion, the milk-barium meal passed through the pyloric sphincter into the duodenum as each and every antral peristaltic wave approached the orifice and, once some of the mixture had passed into the duodenum after the initial gastric delay, there seemed to be a perfectly orderly peristalsis and an orderly evacuation of the gastric content.

The cream-barium meal, containing approximately 13 per cent fat, required an average of 4.8 hours to empty from the stomach, in contrast to 1.9 hours and 3.1 hours for the water-barium and milk-barium (2.33 per cent fat) meals, respectively (Table 1), verifying the observation that the intensity of the control of the pyloric action is proportionate to the fat content.[9] In a study of the gastric evacuation of adult subjects, Gershon-Cohen and Shay[9] found, roentgenologically, that during the early stages of milk digestion the pylorus appeared to be closed and even spastically contracted with the cream meal, the spasm of the pylorus being so marked that it reflected backward into the antrum and forward into the cap so that all the stomach contracted simultaneously.

The fact that cream causes a retardation in the egress of the meal from the stomach and thereby affects the rate of availability of orally ingested carbohydrate has recently been put into practical use in the care of diabetic patients treated with injections of protamine zinc insulin;[21] for example, a combination of bananas and cream, which produces a slowed gastrointestinal rate, delaying the time of maximum absorption from one to two hours, prevents an overloading of blood sugar and eliminates the precipitous drop in blood sugar concentration produced by carbohydrate alone. Since the activity of the protamine zinc insulin is not manifested for several hours after its injection, the importance of delaying the post-prandial rise in blood sugar by means of sustained absorption is obvious. This delay caused by a fat mixture such as bananas and cream allows the absorptive period to come within the range of insulin activity of the current injection.

The protein meal composed of the baked meat loaf accompanied by water had a different volume and consistency than the other barium meals studied,* and the time required for its ingestion ranged up to thirty minutes. The average gastric emptying time was 5.0 hours as compared with 1.9 hours with the water-barium meal. It is known that protein requires a high gastric acidity for initial digestion; consequently, interest has been centered upon a study of the hydrochloric acid present in the acid chyme and the subsequent pH of the duodenal content upon gastric peristalsis and

* During cooking the water lost was approximately 50 grams. The resulting meat loaf contained, roughly, 10 grams of fat and 20 grams of protein, providing concentrations in the total 250 grams of the meal of approximately 5.5 per cent fat and 7 per cent protein.

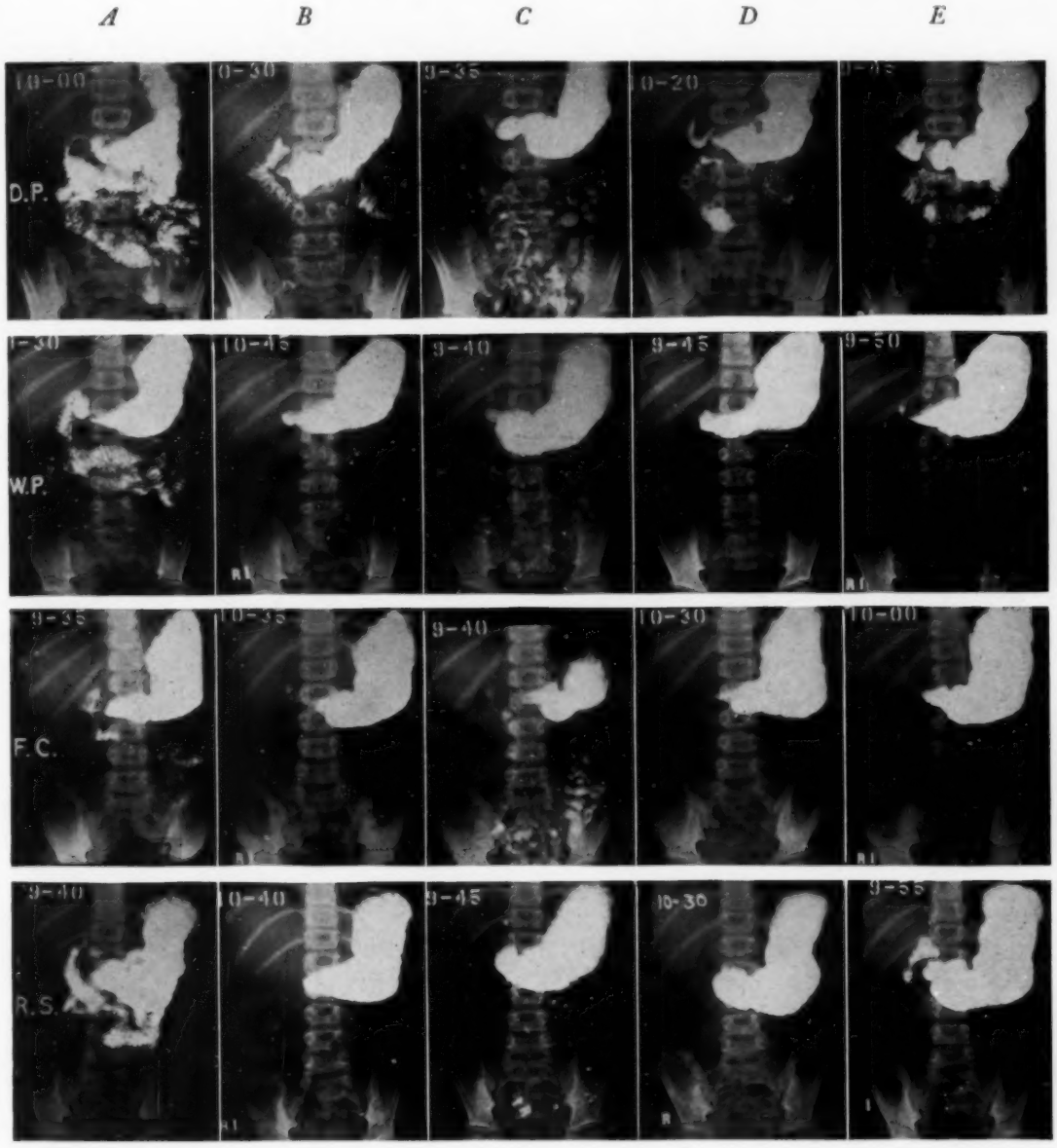

Fig. 1. Twelve minutes after ingestion: *A*, water meal; *B*, milk meal; *C*, meat meal; *D*, cream meal; *E*, carbohydrate meal.

evacuation. Here again the body demonstrates homeostasis to a significant degree, for the excellent investigations of Mann and Bollman and their collaborators[18] have shown that the stomach and duodenum have remarkable power of compensating for marked alterations in their secretory mechanisms. There is an increased acidity of the duodenal content following a protein meal but the normal duodenum has the ability to neutralize the acids from the stomach that reach it, thus permitting an almost unvarying reaction to their content by the jejunum and ileum. It was shown by this group of investigators that, in dogs, after a meal of 100 grams of meat the reaction of the duodenal content during the next hour or two fluctuated within the range of pH 6.4 to 3.5 after which there was a gradual tendency towards neu-

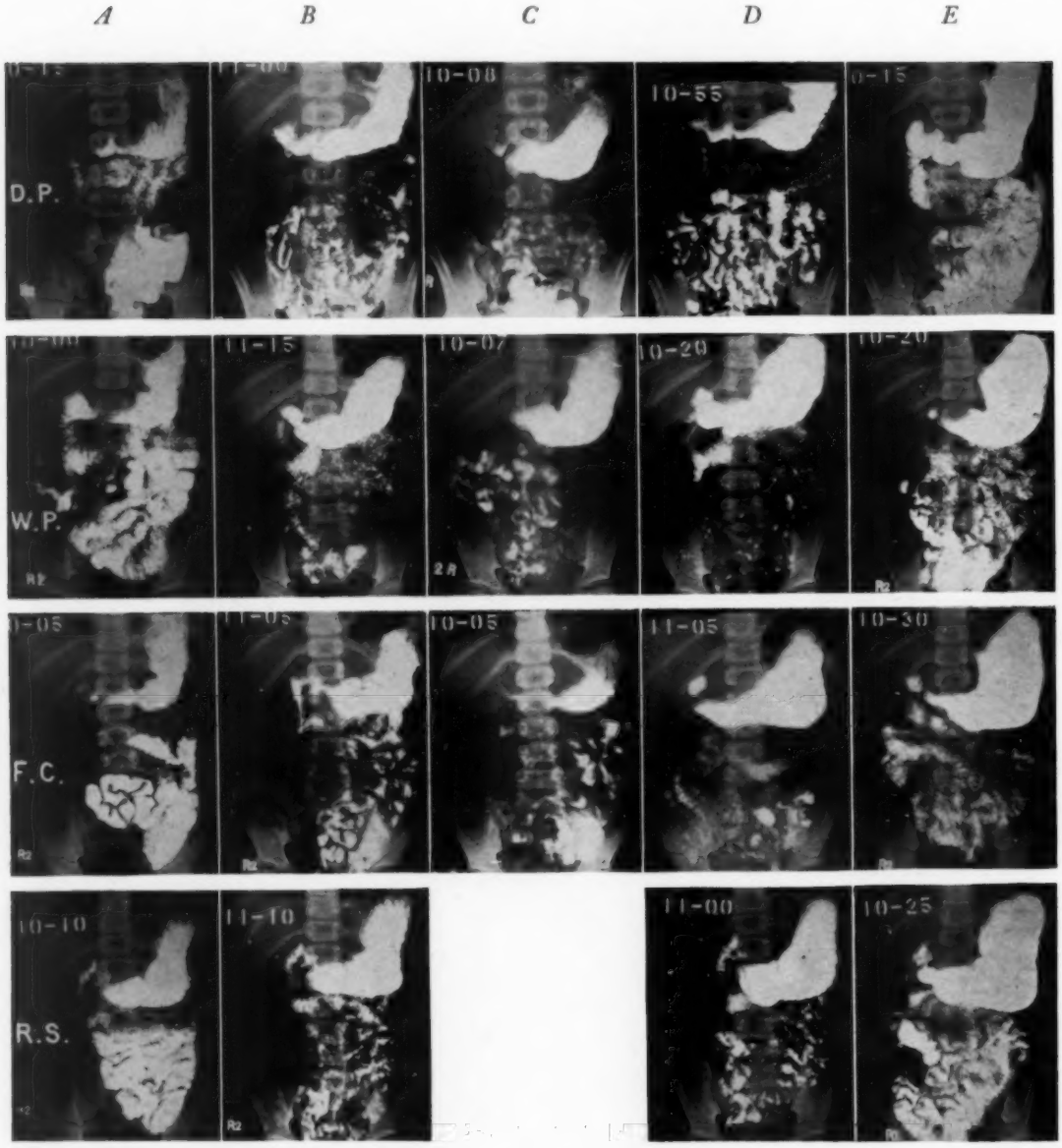

Fig. 2. Forty minutes after ingestion: *A*, water meal; *B*, milk meal; *C*, meat meal; *D*, cream meal, *E*, carbohydrate meal.

trality.[11] Following a carbohydrate meal, the reaction ranged from pH 6.8 to 4.3 and after a fat meal from pH 6.8 to 5.8. The acidity of the duodenum after meals appears to depend largely on the rate and amount of acid formation in the stomach (results which are in agreement with other investigators[6]), the meals modifying the gastric acidity through an inhibitory effect on gastric secretion and motility and the variation in acidity compensated in the duodenum in such a manner as to render the content neutral or slightly acid.

Emptying Time of the Intestines. Our knowledge of the mechanics of the small intestine is still incomplete. From the experimentation thus far carried out, it would seem to be chiefly the action of the muscularis mucosae that keeps the food finely divided so that the digestive juices may

operate as well as act in some manner in the propulsion of the food along the course of the small intestine.

It has long been known that peristaltic waves are visible in the small intestine only when it is somewhat overloaded with a mass of food, though the jejunal and ileal patterns are quite distinct in their appearance. When the food approaches the region of the ileocecal valve, the intestinal movements are much less active and there is considerable massing and overlapping of the shadows and the outline of the intestine in that region is less well defined. The nearer the food approaches the end of the small intestine the less the peristalsis is visible. During roentgenoscopic observations (L.R) a sudden propulsion of the contents of the last few inches of the ileum into the cecum is frequently seen, and this

Fig. 3. Seventy-five minutes after ingestion: *A*, water meal; *B*, milk meal; *C*, meat meal; *D*, cream meal; *E*, carbohydrate meal.

occurs with such suddenness that it leaves us somewhat bewildered as to the exact mechanism which brought it about—whether it is the result of a sudden spasm that "synchronized with the opening of the valve," as suggested by Barclay,[1] or some other mechanism of physiologic propulsion is not clear-cut enough to determine.

the reproductions are arranged so that comparisons of the differences of reaction to different meals in the same child may be illustrated. The widest range of individual difference is represented by these 4 children and all observations made from their roentgenograms represent the group adequately. Each child has a definite response typical of the individual while at the same time

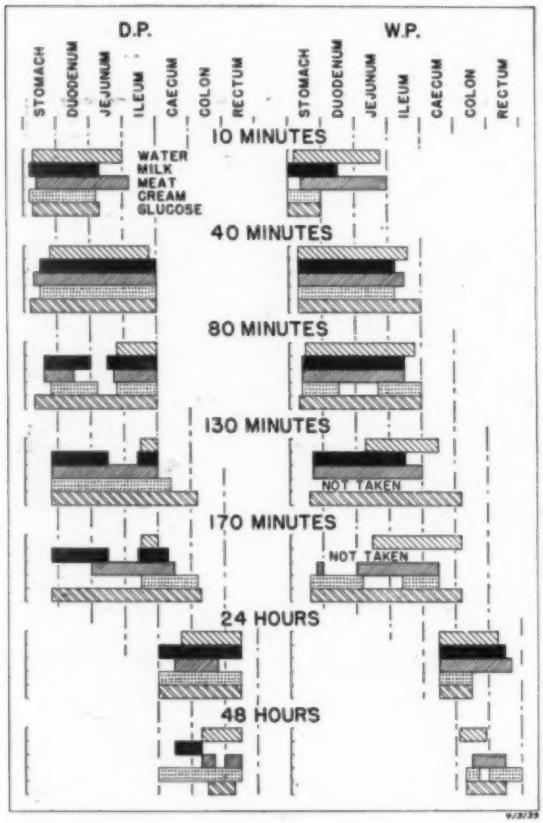

CHART I

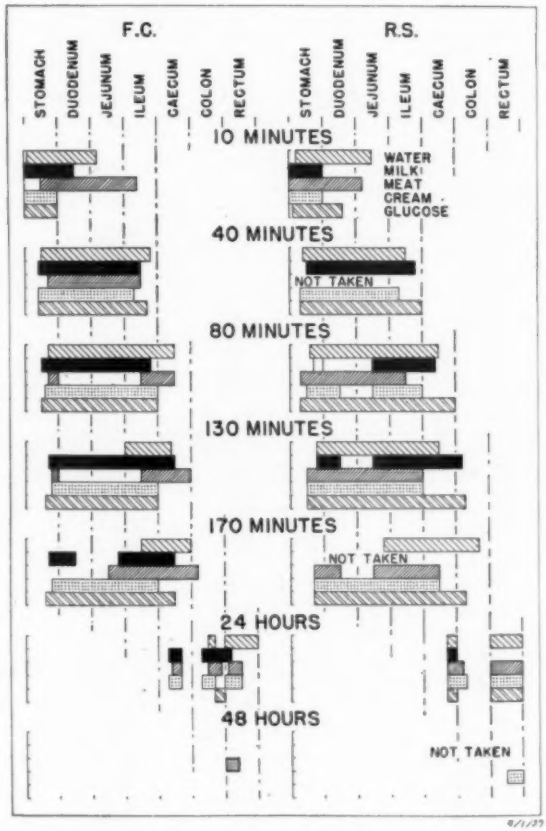

CHART II

Under normal conditions there is no absorption of carbohydrate, fat or protein from the stomach.[3,33] The real region of absorption is the small intestine. These substances are generally digested and absorbed by the time the chyme reaches the ileum. If any undigested food enters the large intestine, however, it *may* be absorbed there.

In the series of roentgenograms for the children who received all of the test meals, each child shows a greater variation in response to the different meals, results which are in agreement with those of Ladd with infants.[14] Consistently, the most rapid motility is shown by the water meal and the least by the meat and cream meals. To clarify and bring the clinical estimations together more closely the relative motility of the 4 children in response to the five different meals has been represented in Charts I and II. An inspection of the charts

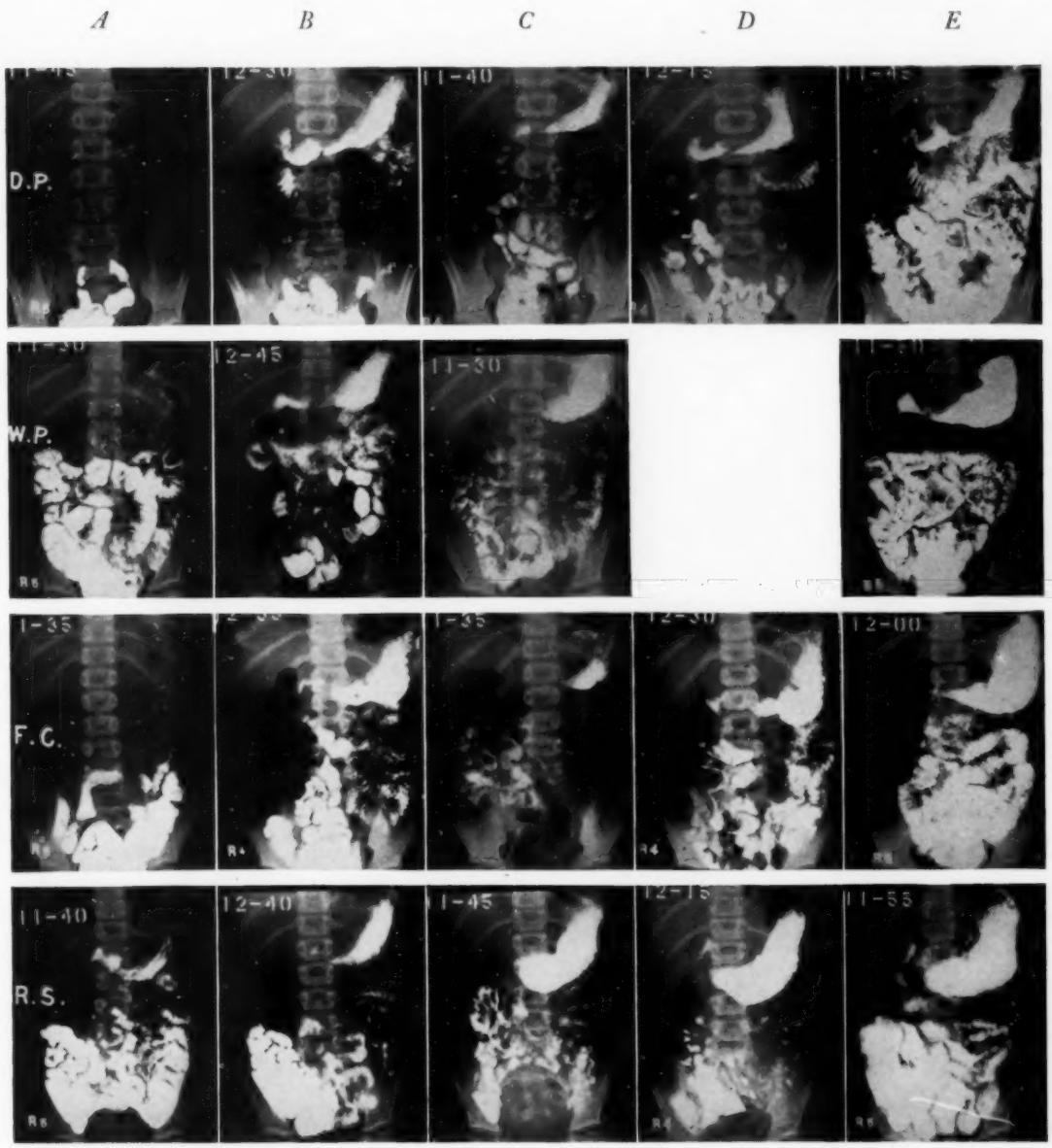

Fig. 4. One hundred and thirty minutes after ingestion: *A*, water meal; *B*, milk meal; *C*, meat meal; *D* cream meal; *E*, carbohydrate meal.

seems to indicate that the children with the most rapid gastric motility have the least rapid intestinal motility, and the children with the least rapid gastric motility have the most rapid intestinal motility.

The initial roentgenograms (Fig. 1) portray the logical intestinal response consequent to the reactions of the stomachs to the various types of the test media. Due to the gastric inhibition only one of the children (D.P.) emitted some of the milk and cream meals into the jejunum during the first twelve minutes after ingestion. The same child and one other (R.S.) show some of the carbohydrate meal in the jejunum after the same interval. The typical, regular progress of the water meals is apparent. Although the protein meal had advanced farther into the tract twelve minutes after completion of ingestion of the meal, the

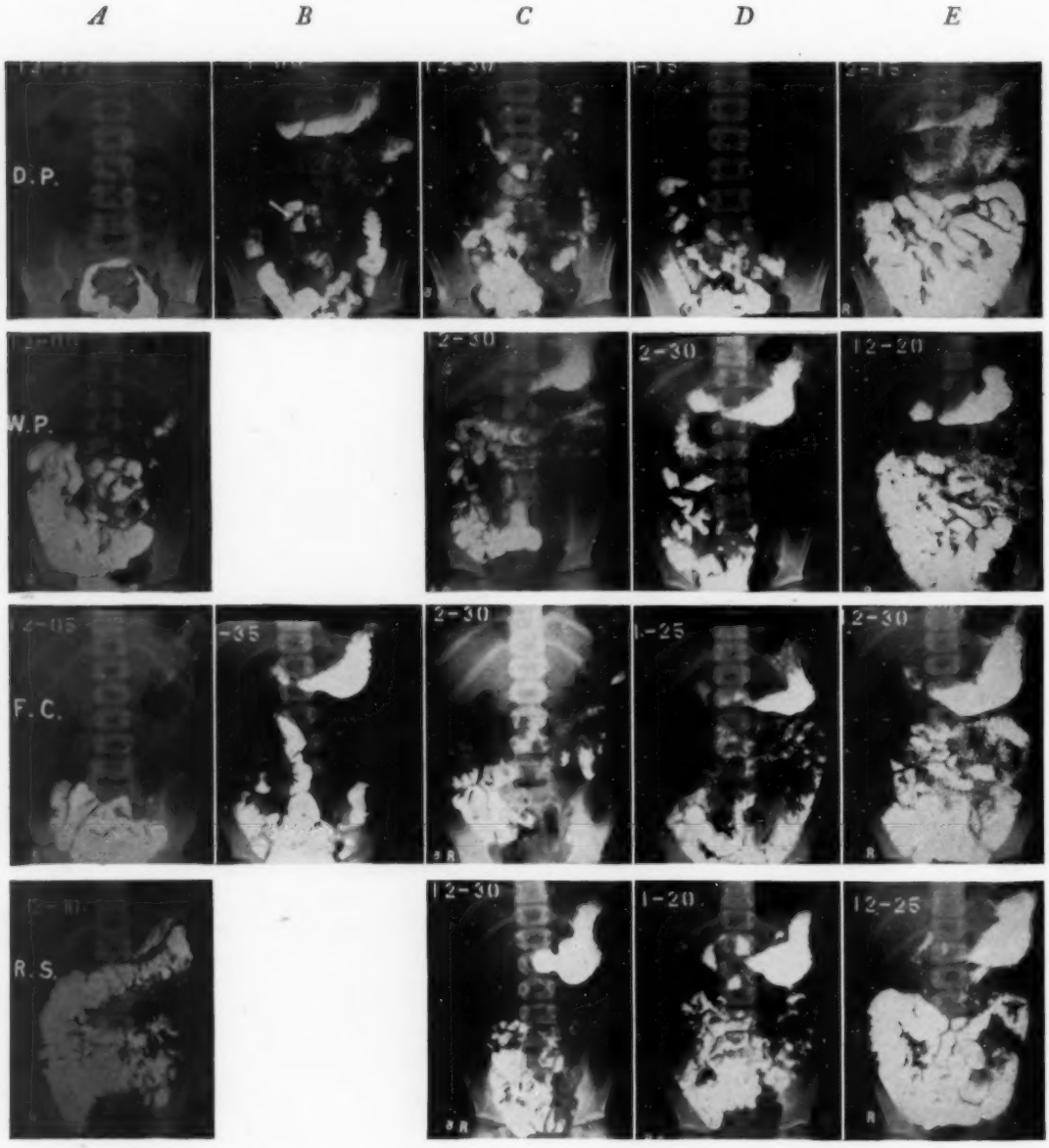

Fig. 5. One hundred and seventy minutes after ingestion: *A*, water meal; *B*, milk meal; *C*, meat meal; *D*, cream meal; *E*, carbohydrate meal.

longer time allowed for consumption of the unappetizing mixture undoubtedly contributed to the result shown.

After forty minutes (Fig. 2) the water meal of each of the subjects was somewhat massed in the terminal ileac loops; the stomachs were half empty or more; and the rugae were clearly outlined. The leading portions of the milk meals had progressed approximately as much as the water meals but in not as great quantity and the roentgenograms show an entirely different pattern. The meat meals showed the individual pattern indicated on the initial exposures but in a greater concentration. The cream meals had advanced as far as the ileum in all cases but wider individual variations were shown with this meal and less of the material was emptied from the stomach than with any of the other meals. For all the subjects the glucose meals indicated a much greater dispersion of the barium in the

duodenum, jejunum and ileum, perhaps due to the large addition to the volume of liquid in which the barium was distributed. The pattern of the glucose mixture was more like that of the water meal than any of the others.

Approximately seventy-five minutes after ingestion (Fig. 3) the water meals had made consistent progress, and the motility shown for the different children was at the same relative rate for each. The milk meals also showed continuous progress although apparently there was a cessation or slowing down in the emission of stomach content for all of the children except W.P. This inhibition is even more pronounced with the meat meals, with which practically all gastric emptying seems to be stopped at this interval, with a tendency for the meal to accumulate in the lower ileum and cecum,

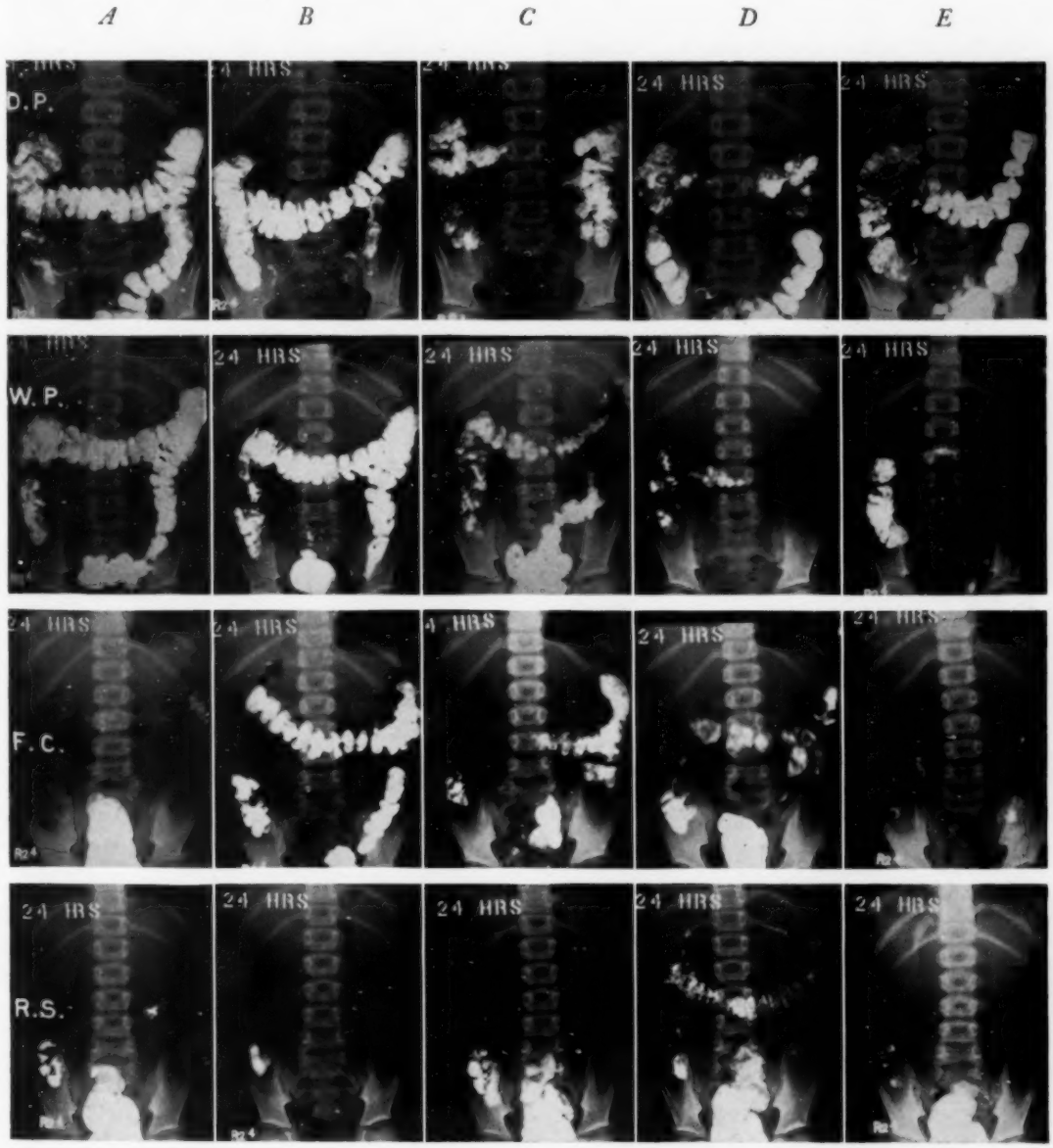

Fig. 6. Twenty-four hours after ingestion: *A*, water meal; *B*, milk meal; *C*, meat meal; *D*, cream meal; *E*, carbohydrate meal.

FIG. 7. Forty-eight hours after ingestion: *A*, water meal; *B*, milk meal; *C*, meat meal; *D*, cream meal; *E*, carbohydrate meal.

leaving the jejunum entirely empty. The same effect was quite pronounced with the cream meals which accumulated in masses of greater density than those of the meat. After this interval the glucose meals were much more widely diffused throughout the entire length of the small intestine.

In Figures 4 and 5 the progress of the different meals is consistent with the indications of the preceding exposures. In these illustrations the roentgenograms of the 4 children illustrate clearly the enormous increase in quantity of the glucose meal; the rapid, orderly progress of the water meal; and the inhibitory gastric effect produced by the milk and cream meals. The individuality of each child's response is emphasized by the roentgenograms of D.P. and R.S. after 130 minutes (Fig. 4).

The twenty-four and forty-eight hour reproductions (Figs. 6 and 7) indicate all the meals in the cecum, colon, or rectum

twenty-four hours after ingestion. No consistent variations may be seen in the response to different meals; individual response is quite obvious. These alterations in the response would be expected, due to the fact that in the large intestine the material has been digested and fecal formation and motility are dependent upon additional physiologic influences more than upon the source of the material.

SUMMARY

The gastrointestinal response of healthy children to test meals of barium in water, milk, cream, meat and carbohydrate media was determined roentgenologically as one of many coördinated studies designed to present a more complete evaluation of the processes involved in chemical growth. The gastrointestinal investigations were made following eight months of intensive metabolic study of the same children, who had been selected by thorough physical and mental examinations as representative of average, healthy children. The subjects lived in an adequate "home" environment and their habits of diet and elimination were well standardized.

The different test meals were studied at least one week apart and were ingested in the morning into a food-empty stomach. Roentgenograms were exposed immediately after administration of the meals and each half hour or hour thereafter until the stomachs were empty. During this interval (four to eight hours) the children played indoors but were restrained from ingesting any other food or liquid. Additional roentgenograms were obtained twenty-four, forty-eight, and, when necessary, seventy-two hours after the initial examination. The 300 exposures procured clearly illustrate variations: among individuals' responses to the same meal; in the individual's responses to different meals; and in the responses of the different sections of the tract.

The water meals produced the most consistent and constant reactions within both stomachs and intestines. The milk, cream, and carbohydrate meals were all subject to an initial delay in gastric emptying. In comparison with the progress of the water meals through the intestine, the milk mixtures were slightly delayed and the cream meal considerably retarded. The meat meals, containing both protein (7 per cent) and fat (3.5 per cent), did not produce the same delay in gastric emptying shown by the cream meal and made more rapid progress through the small intestine until the leading portions reached the terminal ileac loops. At this time the protein-fat mixtures seemed to exert a stronger gastric inhibition than did the cream media. Following the initial delay in gastric emptying the carbohydrate meal filled the entire small intestine very rapidly and at the same time the stomach increased in size, indicating the extreme rapidity of action of a humoral mechanism which reacts to bring stomach contents to isotonicity by osmotic induction of water into it.

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Vol. 43, No. 4

EFFECT OF INJECTIONS OF DISTILLED WATER ON THE GROWTH OF IRRADIATED MOUSE SARCOMA 180*

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IN A PREVIOUS communication,[4] it was shown that tumor transplants of mouse sarcoma 180 when irradiated *in vivo* showed no regression with a dose of less than 500 roentgens, and very few with less than 750 r. With a dose of 1,000 r, about 50 per cent of the cases showed regression. With a dose of 1,500 r, about 85 per cent of cases showed complete regression, but with a dose greater than 1,800 r, tumor regression occurred in 100 per cent of the cases.

If tumors are treated with 1,500 r while in the host, and immediately removed and implanted into normal mice, about 80 per cent will grow progressively as in the case of tumor fragments irradiated *in vitro* with the same dose of roentgen rays. If they are allowed to remain in the original host for twenty-four hours before re-implantation, only 50 per cent will take while if left three days before re-implantation, only 20 per cent will result in takes. In order to get complete inhibition of growth it is necessary to leave the tumor in the animal for six days or longer.[5]

Chambers and Grand,[1] and Sugiura and Cohen,[6] using the tissue culture technique, recently reported additional information concerning the viability of irradiated tumor tissue. Tumors (mouse sarcoma 180) irradiated *in vivo* with a dose of 1,500 r and then removed within twenty-four hours and cultured, generally will grow progressively in culture in all cases. If the irradiated tumors are allowed to remain in the original hosts for three days before culturing, only about 33 per cent will show slight migration and growth of sarcoma cells. On the other hand, complete inhibition of sarcoma growth will occur in those left in the original animals for five days or longer.

The variations in the viability of tumor fragments at different intervals after irradiation can be correlated with changes in their histological appearance. Tumors remaining seventy-two hours in the host after irradiation with 1,500 r show markedly swollen cells. The volume of these swollen cells is approximately twelve times that of the normal tumor cells (Fig. 1). Experimental evidence has indicated that the swelling of tumor cells is not a post-mortem change. Therefore, it is our belief that the death of the tumor cells may be due to swelling.

Recently Failla[2] advanced the "fluid flow" theory concerning the biological action of radiation. According to Failla, roentgen rays tend to increase the number of electrolytic ions in the cytoplasm of irradiated tumor cells. Such a change would disturb the osmotic equilibrium and available fluids would tend to enter through the semipermeable cell membrane to equalize the ion concentration on both sides of the membrane. Swelling generally follows, which, if sufficient, disrupts the cell. Failla suggested that the lethal effect of roentgen rays is due possibly to an initial swelling and consequent dilution of the cytoplasm which interferes with the normal physiological processes. According to this theory it should be possible to increase the radiosensitivity of a tissue by increasing its circulation or by decreasing the osmotic pressure of the surrounding extracellular fluids. This can be done by injecting water into the tumor following irradiation. The following experiments were carried out with the object of testing this supposition.[3]

* Presented before the Third International Cancer Congress, Atlantic City, N. J., Sept. 11–15, 1939.

Effect of Water upon the Growth of Non-irradiated Mouse Sarcoma 180. As a preliminary study, we determined the extent of the deleterious action of distilled water upon the development of transplanted tumors (mouse sarcoma 180) in mice. This was done because the results of our *in vitro* experiments[7] showed that the growth capacity of mouse sarcoma 180 was markedly destroyed (60 per cent inhibition) when the transplants were immersed in distilled water for twenty-four hours at 4–5°C. before being placed in the hosts. On the other hand, the proliferating capacity of mouse sarcoma 180 was unaffected by water when it contained salts of a Locke-Ringer solution in an isotonic amount. Furthermore, the growth capacity of mouse sarcoma 180 was inhibited 69 per cent at pH 5.0, and 61 per cent at pH 9.0. Tumor fragments immersed in solutions at pH 6.0, 7.0 and 8.0 for twenty-four hours at 4–5°C. grew normally when implanted into mice.[8] The pH of ordinary distilled water is generally 5.5.

Subcutaneous inoculations of tumor tissues into healthy young adult mice (Bagg albino mice and Rockland albino mice), usually weighing from 22 to 25 gm., were carried out by the usual trocar method. The transplants showed occasional spontaneous regression, such cases representing about 2 per cent of the positive growths (99 per cent). The tumor grows very rapidly (initial size of 2×2×2 mm. to a final size of about 13×18×10 mm.) and kills the animal in about three weeks.

When tumor grafts had grown for about seven days in animals and had attained a diameter of 5 to 8 mm., they were injected with sterile distilled water with a dose of 0.5, 0.75 or 1.0 cc., from two to four times daily for three to seven successive days. The injection of water was done with

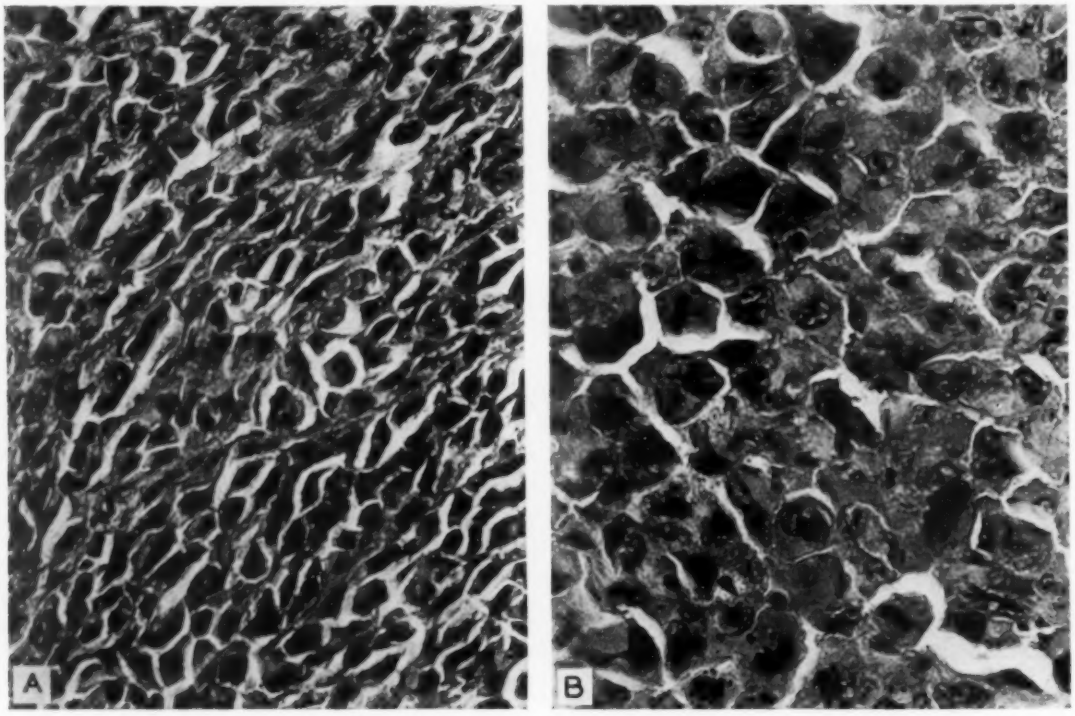

Fig. 1. Showing the relative sizes of non-irradiated and irradiated tumor cells. Photomicrographs of sectioned material were made at the same magnification. *A* is untreated mouse sarcoma 180; *B* is mouse sarcoma 180 irradiated *in vivo* with a dose of 1,500 r and allowed to remain three days in the host.

a No. 24 gauge needle and by advancing the needle point in three directions within the capsule. The animals were then allowed to live as long as they would. They were fed upon Purina laboratory chows and lettuce, with as much fresh water as they would take.

The results showed that the repeated injections of sterile distilled water had no apparent influence upon the growth of transplanted tumors. The autopsies did not reveal any increase in the percentage of metastases, either local or distant, in the water injected animals over the non-treated control animals. This study included five groups of experiments involving a total of 50 tumors.

Histological examinations of a number of water treated tumor tissues show no definite changes in the structure except for larger necrotic areas than in non-treated tumor tissues (Fig. 2). The tumor cells appear to be viable. There is no noticeable cell swelling.

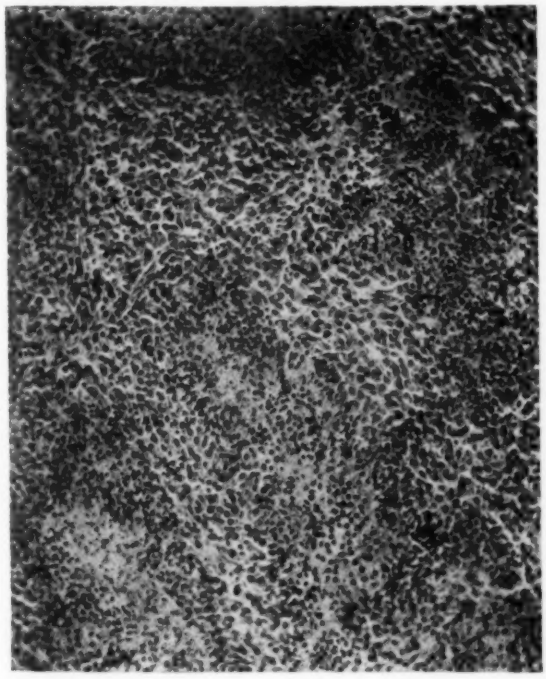

Fig. 2. A section of a water injected tumor showing no apparent alteration of the individual cells. There are, however, many scattered and irregular areas of cell degeneration.

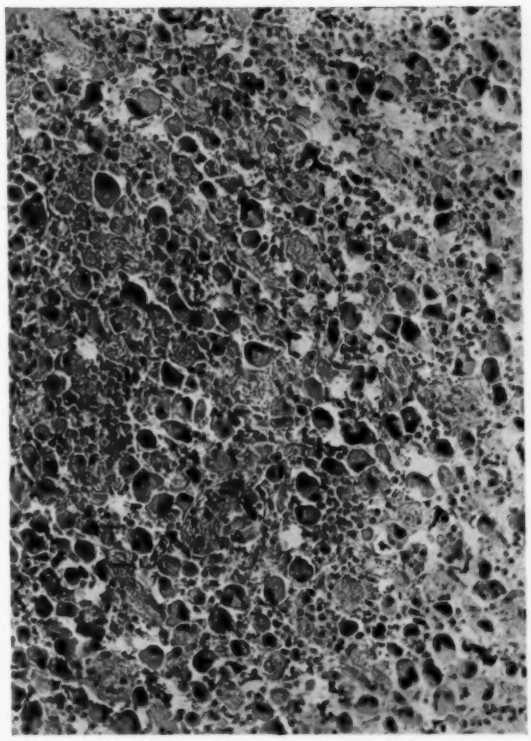

Fig. 3. Irradiated mouse sarcoma 180, showing degenerating tumor cells and marked lymphocytic and polymorphonuclear infiltration. No viable tumor cells can be seen in the sections.

Effect of Water upon the Growth of Irradiated Mouse Sarcoma 180. Histological examination of a number of the irradiated tumors (1,500 r) shows changes in the general structure during the first three to five days. Then the tumors undergo necrosis. Those remaining seven days in the original irradiated animals are composed of degenerating tumor cells, in which nuclei are absent or pycnotic (Fig. 3). Tumors receiving smaller doses of radiation show changes in the histologic picture but to a lesser degree.

In the present study, we used the doses of 500, 750 and 1,000 r to determine whether appreciable changes in radiosensitivity could be produced by supplementary treatment with water. It has been shown that under normal conditions of irradiation these doses produced 3, 15 and 50 per cent tumor regressions, respectively.

When tumor grafts (mouse sarcoma 180)

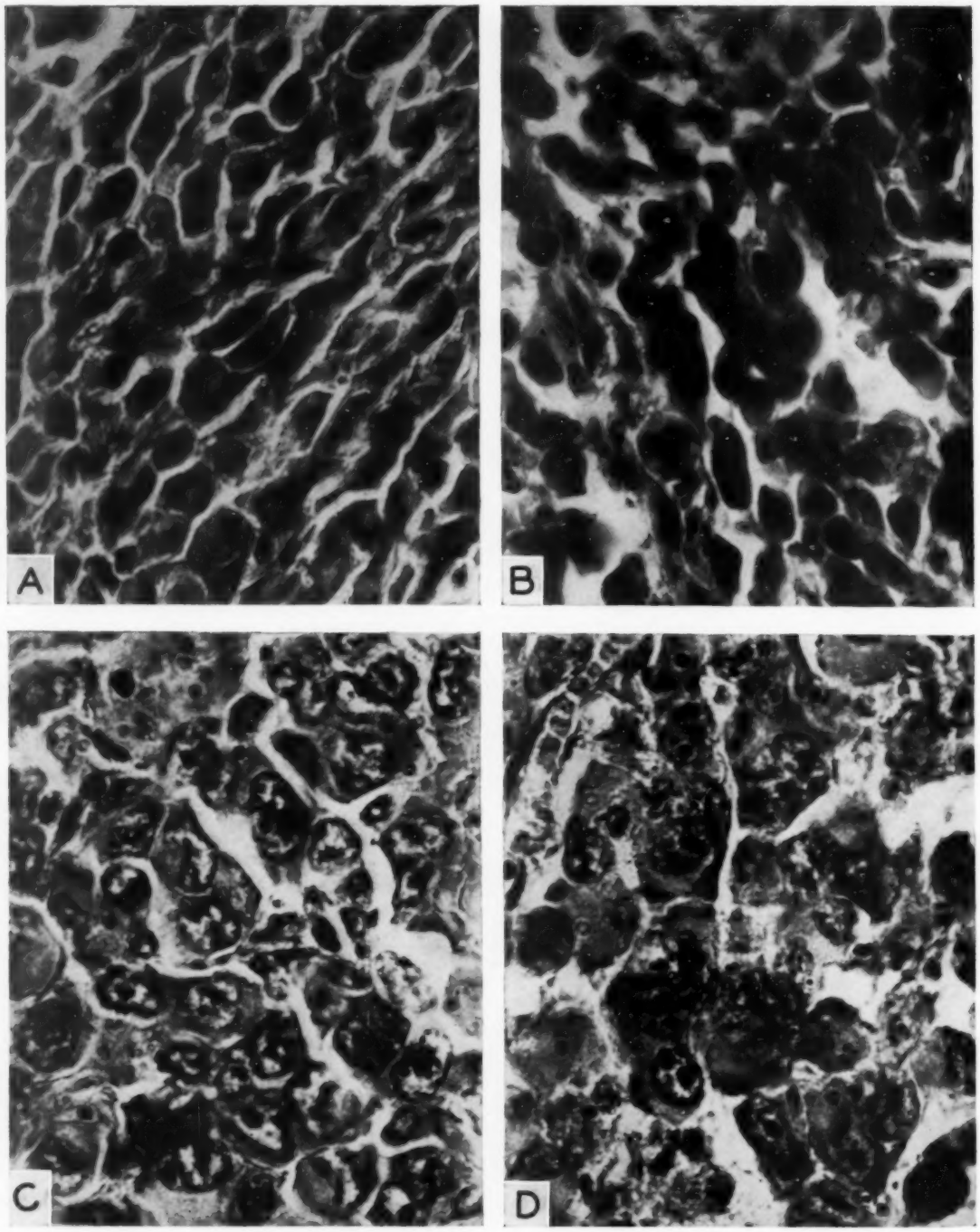

Fig. 4. Showing changes in histologic appearance in irradiated and irradiated and water treated tumors. Photomicrographs of sectioned material were made at the same magnification. *A*, untreated mouse sarcoma 180; *B*, treated with water alone; *C*, treated with roentgen rays alone (1,000 r); *D*, treated with roentgen rays (1,000 r) and water.

had grown for about seven days in animals and had attained diameters of 5 to 8 mm., they were irradiated with a dose of 500, 750, or 1,000 r in the same manner as that previously described.[4] The conditions of irradiation were as follows: 200 kv.,

30 ma., 0.5 mm. copper and 1.6 mm. aluminum filter, 50 cm. distance to tumor, with an intensity of 54.4 r/min.

Then 0.5 cc. of sterile distilled water was injected into the tumor from one to four times daily for two to six successive days. The results are presented in Table 1.

TABLE I

EFFECT OF INJECTIONS OF WATER ON THE GROWTH OF IRRADIATED MOUSE SARCOMA 180

No. of Tumors Used	Dose in Roentgens	Amount of Water Used at Each Injection (cc.)	No. of Daily Injections	No. of Days Injected	Per Cent of Tumor Regression
36	500	0	0	0	3
20	750	0	0	0	15
40	1000	0	0	0	50
6	500	0.5	1	6	0
6	750	0.5	1	6	17
6	1000	0.5	1	6	33
12	500	0.5	2	2–3	8
12	750	0.5	2	2–3	25
12	1000	0.5	2	2–3	50
16	500	0.5	2	5–6	25
20	750	0.5	2	5–6	45
24	1000	0.5	2	5–6	75
22	500	0.5	4	4–5	36
28	750	0.5	4	4–5	61
30	1000	0.5	4	4–5	93

From the data in Table 1, it will be seen that injection of distilled water markedly increased the radiosensitivity of the tumor, especially when given as 0.5 cc. of water twice on the same day of irradiation and four times daily on three to four successive days. Thus with roentgen rays and water, 36 per cent tumor regressions with 500 r, 61 per cent tumor regressions with 750 r, and 93 per cent tumor regressions with 1,000 r were obtained. Roentgen rays alone in these doses produced 3, 15 and 50 per cent tumor regressions, respectively. However, injection of water once a day for several days did not change the normal course of tumor regression.

The successfully treated tumors disappeared completely in about twenty days. The time is approximately the same as that of those successfully irradiated with 1,500 r or 3,000 r but without water treatment.

Histological examinations were made on both irradiated tumors and tumors irradiated and followed by water injection (Fig. 4). In the case of 500 and 750 r, the general structure of irradiated and irradiated and water treated tumors was essentially the same. The tumor cells were swollen but appeared to be viable. However, in the case of 1,000 r, those without water treatment appeared to be normal active cells although they were markedly swollen. On the other hand, those receiving 1,000 r and water treatment appeared to be partially degenerated and not active. The swelling of tumor cells was greatest on the third day after irradiation.

Effect of Isotonic, Hypotonic, and Hypertonic Locke-Ringer Solutions on the Growth of Irradiated Mouse Sarcoma 180. The results of the foregoing experiments show that the radiosensitivity of mouse sarcoma 180 is markedly increased by injections of distilled water (a strong hypotonic medium) following local treatment with roentgen rays.

In order to secure further information concerning the water and killing of tumor cells, we did the following experiments.

When tumor grafts (mouse sarcoma 180) had grown for about seven days in animals, they were irradiated with a dose of 500, 750, or 1,000 r. Then 0.5 cc. of isotonic, hypotonic, or hypertonic Locke-Ringer solution was injected into the tumors twice on the same day of irradiation and four times thereafter for four successive days.*

The results showed that repeated injections of the isotonic or hypertonic Locke-Ringer solution, following irradiation with

* An isotonic solution contained 0.15 molecule NaCl, 0.003 molecule KCl and 0.003 molecule $CaCl_2$ per liter. A hypotonic solution contained 0.03 molecule NaCl, 0.003 molecule KCl and 0.003 molecule $CaCl_2$ per liter. A hypertonic solution contained 0.18 molecule NaCl, 0.003 molecule KCl and 0.003 molecule $CaCl_2$ per liter.

a dose of 500, 750, 1,000 r, did not change the normal course of tumor regression. On the other hand, the repeated injection of the hypotonic Locke-Ringer solution following irradiation definitely increased tumor regression (33, 50 and 83 per cent tumor regression, respectively). This study included three groups of experiments involving a total of 54 tumors.

SUMMARY

1. The radiosensitivity of mouse sarcoma 180 was increased markedly by injections of distilled water following local treatment with roentgen rays.

2. Repeated injections of an isotonic or hypertonic Locke-Ringer solution into the tumors following irradiation with a dose of 500, 750 or 1,000 roentgens did not change the normal course of tumor regression. On the other hand, injections of a hypotonic Locke-Ringer solution following local treatment with roentgen rays definitely increased tumor regression.

3. Daily repeated intratumor injections of sterile distilled water had no apparent influence upon the growth of tumors.

I wish to express my thanks to Dr. G. Failla for his valuable suggestions during the course of the work.

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Vol. 43, No. 4

EFFECT OF IRRADIATION ON NORMAL AND METASTATIC LYMPH NODES*

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RELATIVELY few histologic studies have thus far been made on the effect of heavy radiation treatment upon normal and metastatic lymph nodes. Leaving out of consideration certain radiosensitive tumors, such as lymphosarcoma or transitional cell oral carcinoma, we find almost universal disappointment, regardless of the amount of radiation employed, with the results obtained in the metastatic lymph nodes of a squamous cell carcinoma. Regressions are occasionally found but they are almost always only temporary. It would seem, as Jacox has stated, that the histologic study of early cancerous deposits in lymph nodes fails to reveal evidence of wholesale destruction of tumor cells and that lymphoid tissue provides a highly fertile soil for the growth of most carcinomas.

In 1904 Heineke experimented with radiation effects on the lymph nodes of pigs, rabbits and dogs and found destruction of a greater part of the lymphocytes in and around the follicles. He stated that the lympocyte is among the most vulnerable to roentgen rays. This work was later confirmed by Menetrier and Touraine. This was generally accepted as true until Quick and Cutler in 1925 came to very different conclusions. In 40 cases of oral carcinoma they studied the lymph nodes in the neck removed subsequent to heavy irradiation. Their experience was that the immediate effect of such irradiation was an increase in the mitotic figures in the germinal follicles and evidence of enlargement with hyperplasia. They conclude: "The histological picture observed in these cases is very striking. The lymphoid tissue is resistant, the lymphocytes retain their cell outline, the nuclei show light striations but retain their form. No karyolysis nor karyorrhexis is evident. The lymphoid follicles stand out prominently and appear enlarged and edematous. The germinal centers contain numerous mitotic figures; the endothelial cells appear normal." They state that Ewing had repeatedly observed that normal lymphoid tissue resists large doses of radiation. Quick and Cutler raise the question whether this reaction is perhaps indicative of a state of heightened resistance against invasion by the tumor growth. This stimulating effect of radiation on lymphoid tissue was so much at variance with the experience of others that some special factors may perhaps have been responsible. One of these, mentioned by Quick and Cutler, may be the marked infection of the primary tumor in the mouth produced by the radium application. The writers do not state what interval of time elapsed between irradiation and the lymph node excision. It is possible that if this interval was a short one, the final destructive effect of heavy irradiation upon the lymph follicles might not yet have been manifest. I could find no reports substantiating the findings of Quick and Cutler but several recent reports contradicting their findings.

Welsh in 1934 found that lymph follicles were readily destroyed by heavy irradiation. Holthusen, in an article on the biological effect of roentgen rays, writes: "The lymph follicle shows a greater radiosensitivity but at the same time also a greater capacity for regeneration, and from a few resistant cells in a relatively short time the obliterated spaces of the reticulum of an irradiated lymph node can again become filled."

For many years I have been engaged in a systematic study of the tributary lymph nodes removed in cases of cancer of the

* Read at the Twenty-fourth Annual Meeting, American Radium Society, St. Louis, Mo., May 15–16, 1939.

cervix and cancer of the vulva. These nodes are those of the pelvic cavity and the inguinofemoral group. It is of course possible that what applies to this part of the body is not universally true, but any marked difference in tissue reactions seems unlikely. This study is based on glands removed in 113 cases of iliac lymphadenectomy for Stage II (League of Nations' classification) cancer of the cervix, 4 obturator, external iliac, ureteral, right or left) (Fig. 1).

From an experimental viewpoint, it was a fortunate circumstance that since October, 1930, when I did my first iliac lymphadenectomy for Stage II cervical cancer there has been a progressive increase in the amount of preliminary roentgen therapy. Up to May, 1934, preliminary irradiation was practically never given. For the follow-

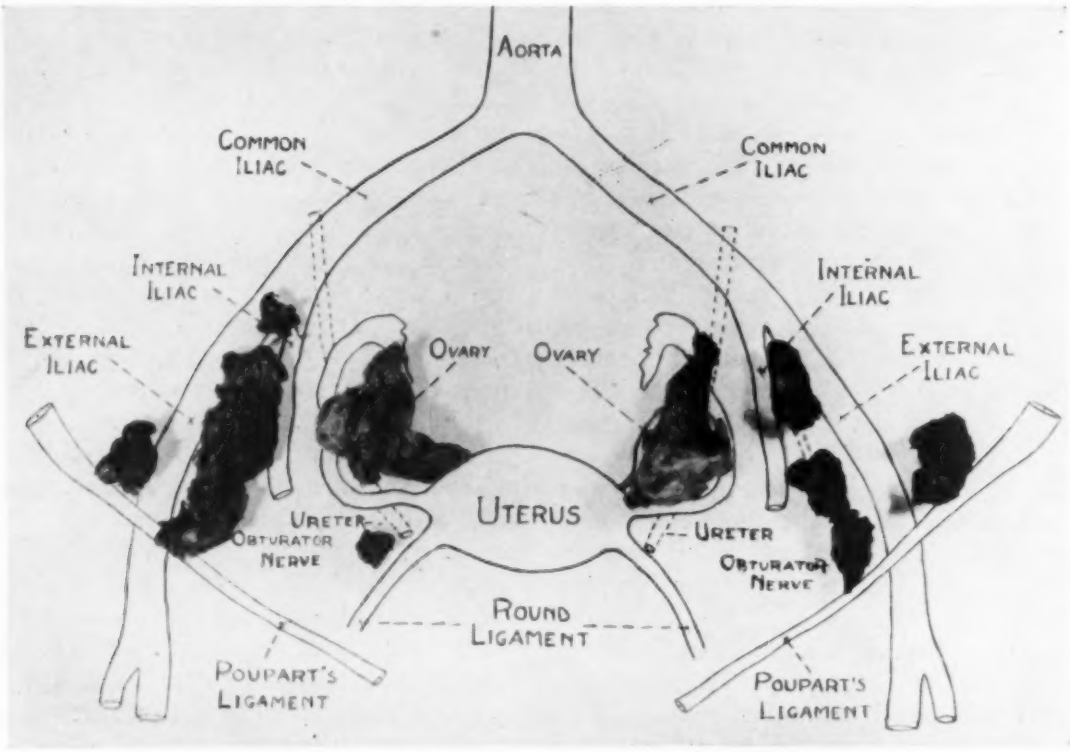

Fig. 1. Anatomic distribution of iliac lymph nodes removed surgically.

Wertheim hysterectomies with gland removal and 60 double-sided Basset lymph node operations associated with cancer of the vulva. In some of the earlier vulvar cases not all sections were saved for study, but a total of 1,039 glands were subjected to individual histologic review. Since none of the 381 vulvar glands were given preliminary irradiation, they serve only as a control. A total of 658 glands was removed in the cervix cases. Each set of glands on removal was placed in a special bottle labeled with its anatomic site (hypogastric, ing two years, 1934–1936, the average dose was only 2,400 r. From 1936 to 1938 this was increased to a total of 5,600 r, and in the past twelve months the usual dose has averaged 7,000 r. A study of the glands with lymph follicles showed a striking difference during these four periods, as seen in Table 1.

The drop from 77 per cent to 14 per cent of glands containing follicles is certainly very striking. As a rule, the interval between the conclusion of the deep roentgen treatments and the removal of the

lymph nodes was about three to four weeks. Where larger amounts of radiation were employed, there was during this interval definite regression and clearing up of the cervical carcinoma. To a slight degree the reduction of infection in the cervix may have decreased the number of germinal follicles in the glands, but could hardly have caused their complete elimination. It should also be mentioned that in recent years the total number of glands removed has been increasing, including a few that normally contain fewer follicles. Neither of these factors is of sufficient importance,

Table I

Years	Average Dose	Follicles Present	Follicles Absent	Follicles Present per cent
Oct., 1930–May, 1934	none	60	18	77
May, 1934–May, 1936	2400	37	56	40
May, 1936–May, 1938	5600	75	212	26
May, 1938–May, 1939	7000	24	151	14

however, to explain the very definite decrease in germinal follicles in glands that received heavy irradiation. I know of no investigation on this subject that has heretofore used exact methods in arriving at conclusions. There is great variation in the histologic picture of lymph glands in different individuals and even in the same individual. Unless each gland is separately reviewed and the percentage of those containing follicles calculated on a large scale, deductions cannot fairly be drawn. A point of further interest was that when we compared the germinal follicles in non-irradiated glands with follicles that had been irradiated, marked differences were noted in many cases (Figs. 2 and 3). In the non-irradiated glands, the follicles had a definite circular or ovoid outline with a rim of several rows of small, deeply staining lymphocytes surrounding the epithelioid cells in the center of the follicle. In the irradiated glands this lymphocytic capsule

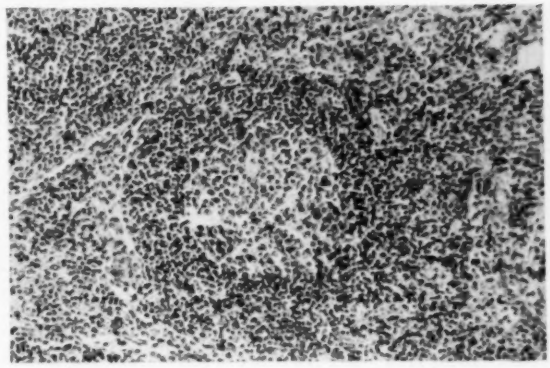

Fig. 2. Non-irradiated lymph node with normal germinal follicles.

of the follicle was often broken and the germinal cells showed definite evidence of partial liquefaction. This disintegration of the follicles can probably be considered as due to an irradiation effect. All in all, therefore, we can fairly conclude that irradiation produces a destruction of the germinal follicles in pelvic lymph glands in direct proportion to its intensity.

The question naturally arises as to the permanency of this destructive effect. Holthusen says that there is an inherent capacity for regeneration of follicles in such irradiated glands. Some confirmation of this statement was to be found in our lymph node studies. Taking only the 47 cases since May, 1936, those in which a destructive dose over 5,600 r had been given, I found that in 7 cases the lymph node removal had for special reasons not

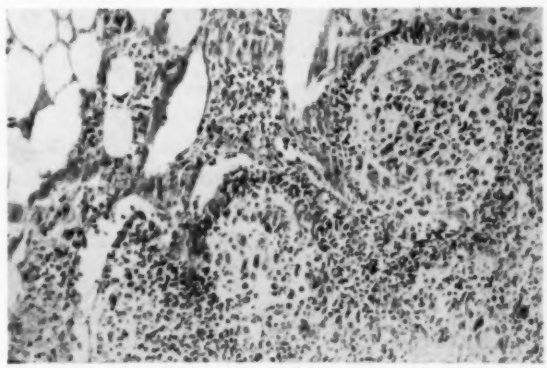

Fig. 3. Irradiated lymph node with disintegrated follicles.

been done until from three to six months after the irradiation. This should allow sufficient time for regeneration. It was found that although the percentage of follicle-containing lymph nodes in the entire 47 cases during this period was 21 per cent, the 7 cases in which operation was delayed had an incidence of follicle-containing lymph nodes of 41 per cent (14 out of 34 glands). These figures are of course too small to be conclusive, but support the theory of Holthusen regarding such regeneration of the germinal follicles.

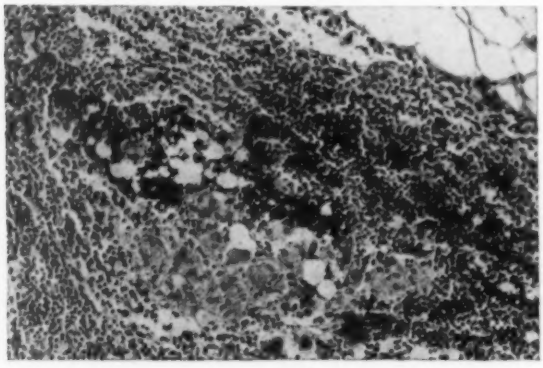

Fig. 4. Minute subcapsular metastasis in a hypogastric lymph node that grossly seemed quite normal.

It would seem, therefore, that deep roentgen therapy applied to the pelvic region produces a definite effect on the normal germinal follicles. Turning now to a consideration of the metastases in these glands, we find that the effect of irradiation is, relatively speaking, insignificant.

Dividing the 113 cases chronologically into the periods of little or no irradiation before operation from October, 1930, to May, 1936, and that of heavy preoperative irradiation (5,600 to 7,000) from May, 1936, to May, 1939, we find that in the 47 cases of the first period cancer metastases were present in the lymph nodes 14 times, equivalent to exactly 30 per cent. During the second period when heavy preoperative irradiation was employed, we found metastases in 22 out of 66 cases, equivalent to 33.3 per cent; slightly more often, therefore, than in the non-irradiated cases. In the total series of 113 cases, 36 showed metastases, an average of 31.9 per cent.

These figures would indicate an accidental variation in the number of cases that showed metastatic lymph nodes but certainly no diminution in their number as a result of preceding roentgen treatment. The histologic study of lymph nodes subjected to heavy irradiation tended to confirm the absence of any appreciable effect on the cancer metastasis. While the cancer cells in the cervix showed marked liquefaction necrosis and vacuolization, the cancer in the lymph node only in rare instances showed even the slightest evidence of destructive changes. The metastases, as a rule, consisted of nests of fairly well differentiated squamous cell carcinoma, often appearing less malignant than the primary tumor in the cervix. Many of these metastases were microscopic in size. Certainly the size and hardness of the lymph glands were not a definite index of the presence of metastasis. Many hard fibrous or hyalinized lymph glands were found free of disease and occasional small soft glands were found to contain nests of cancer cells. Recently I removed a soft hypogastric lymph node only 2–3 mm. in diameter that contained a well developed cancer metastasis (Fig. 4). The more I operate on these cases the more convinced I am that the fact that cancer was not found in a lymph node does not mean that cancer was not present. Only by the tedious process of serial sections of all lymph nodes removed could such a statement be justified. It is false to assume that, because in a little over two-thirds of the cases in which lymph nodes were removed no cancer was found, the operative removal was unjustified. In breast cancer we certainly have ample evidence of the value of routine lymph node removal, regardless of the presence of metastasis. The same has, I think, now been established in the case of cervical cancer. Heretofore the high operative mortality has been held against such surgical removal of lymph nodes. The reason of this high mortality lay, however, not in the

gland removal, but in the associated radical hysterectomy. One thing that I have now proved by my operation of iliac gland removal without hysterectomy in Stage II cancer of the cervix is that it is not a dangerous procedure. In 113 operations of this kind done in the past eight and a half years, only 2 patients have died, a mortality of only 1.77 per cent. Not only has this operative removal of the tributary lymph nodes in border line cervical cancer associated with irradiation of the primary lesion been shown to be safe, but as a larger number of five year cases are now being gathered for report, the ultimate results have been shown to be beneficial. I now have 19 cases operated on over five years ago and 10 of these have survived this period without evidence of a recurrence, *a survival rate of 52.5 per cent.* Three out of the eight cases that showed cancer metastasis in the glands survived the five year period. During this same time, and in the same institution (Barnard Free Skin and Cancer Hospital), 35 cases of Stage II cancer of the cervix were treated by *irradiation alone with a survival rate of only 20 per cent.* In both groups the radiation dosage and methods were identical, yet when the lymph nodes were removed in addition to the irradiation, more than twice as many survived the five year period. It is interesting also to compare my results with the report of Frazell from Healy's clinic. In the the group of border line cases treated over five years Frazell found only 6 living out of 19, a cure of 31.5 per cent. Voltz, in 310 cases of Stage II cancer of the cervix treated by irradiation alone, had a five year survival of 22.3 per cent.

I am willing to grant that the exact number of cures by this iliac gland removal may fluctuate somewhat in later reports. It may fall as low as 40 per cent, but certainly thus far we can fairly conclude that until newer methods of eradicating metastases in lymph nodes by irradiation are found, surgical ablation of these glands most commonly involved is not only justified, but definitely to be recommended.*

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* For discussion see page 571.

RADIUM TREATMENT OF CARCINOMA OF THE CERVICAL STUMP*

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SINCE Chrobak,[1] in 1896, first called attention to cancer developing in the cervical stump after subtotal hysterectomy as a definite clinical entity, a considerable amount of literature has evolved on this important subject. A great many excellent articles have been devoted to the incidence, prevention and treatment of this serious condition. C. H. and C. W. Mayo,[2] Masson,[3] Spencer,[4] von Graff[5] and Polak[6] are among the authorities who have held the belief that cancer occurs in the retained cervix often enough to justify panhysterectomy instead of the more commonly employed subtotal hysterectomy for uterine myomas or other conditions that require removal of the uterus. In addition, Mayo and Dixon[7] have pointed out that, like the prostate gland, the cervix may become a focus of infection; the probability that cancer will develop or that infection will spread from the retained cervix is an argument for panhysterectomy. Masson and Spencer, among others, have stated that the risk of panhysterectomy in skilled hands is little more than that of the conservative operation, especially considering the potentialities of the retained cervix for the development of malignant lesions.

On the other hand, other authorities have considered the incidence of cancer of the retained cervix too small to overbalance the greater surgical risk of panhysterectomy. Baer,[8] Scheffey,[9] Healy and Arneson,[10] Stein,[11] and Leonard[12] are among those who have not favored abandoning the conservative operation for panhysterectomy with the higher mortality rate associated with the latter and the loss of support to the pelvic floor, and so forth. Estimations of the incidence of carcinoma of the cervical stump vary tremendously; for instance, from 0.03 per cent quoted by Scheffey[9] from the German literature after the study of several thousands of supravaginal hysterectomies, to 4.1 per cent quoted by von Graff[5] from radiologic literature. This discrepancy is to be expected, however, because surgeons must trace each operative case, often for more than a quarter of a century, whereas at radium centers in studies of carcinoma of the cervix a much larger series is seen and the lesion often occurs many years after the conservative operation has been performed. Many surgeons such as C. H. and C. W. Mayo[2] and Howard A. Kelly[12] have held the belief that when a supravaginal hysterectomy is performed, a thorough cupping or coning out of the cervical mucosa lessens the possibility of the subsequent development of malignant changes. Polak[6] has disputed this; he has contended that nearly all carcinomas of the cervical stump are squamous cell epitheliomas springing from the mucous membrane of the vaginal portion of the cervix, and that to cone out the cervical canal is not sufficient protection.

We are not qualified to take sides in this argument regarding pelvic operations, but we are interested in the clinical aspects of carcinoma of the cervical stump shown by patients who present themselves for treatment; we are also interested in the treatment that we have been employing in the past, and in the results so far achieved.

At the Fifth International Congress of Radiology in 1937, we[13] presented a survey of treatment and results in 1,491 cases of carcinoma of the cervix in which treatment with radium and roentgen rays was given in this department of the Mayo Clinic from January 1, 1915 to December 31, 1929.

For this present study we have analyzed

* Read at the Twenty-fourth Annual Meeting, American Radium Society, St. Louis, Mo., May 15–16, 1939.

in respect to treatment and results the cases of carcinoma of the cervical stump contained in that group with the addition of 7 cases in which treatment was given in 1930.

Adding the cases encountered in 1930, there were 1,676 patients, who had carcinoma of the cervix, referred for radium treatment. A preliminary survey revealed that in the total of 1,676 cases there were 108 cases of carcinoma of the cervical stump. However, by rejecting those patients not treated at the Mayo Clinic or patients who had only a biopsy and palliative cauterization performed, in the early days of radiologic practice, a total of 99 patients with this diagnosis is left.

Another differential problem was encountered. As Schulze,[14] Branscomb,[15] Spencer, and others have pointed out, carcinomas may be overlooked at the time of the initial operation. Spencer, with Noble and Schlottländer,[4] examined 900 myomatous uteri removed by the method of panhysterectomy, and found, in 2 per cent of the specimens, carcinoma of the cervix which had been previously overlooked. In addition there is the possibility of a metastatic carcinomatous lesion or a recurrent lesion in the cervical stump from the primary site of an excised cancer of the fundus uteri or ovary. These possibilities present a complicated therapeutic problem and prognosis, just as the treatment and prognosis of a primary lesion of carcinoma of the breast, for instance, differs from treatment and prognosis of a distant metastatic lesion from carcinoma of the breast. Hence, to eliminate as far as possible overlooked epitheliomas of the cervix and metastatic lesions from fundal and ovarian cancer, we adopted Sharples'[16] dictum, that if carcinoma is not diagnosed in the retained cervix until two years after the subtotal hysterectomy, it is probably a genuine instance of malignancy of the cervical stump. This view was also advanced by Nuttall and Todd,[17] who termed carcinomas discovered less than two years after subtotal hysterectomy as "coincident cases," or dual carcinomas and if discovered more than two years afterward, as probably genuine cases of stump carcinoma.

TABLE I
INCIDENCE

Patients with carcinoma of the cervix, treated with radium (1915 to 1930, inclusive)	1676
Of this group, diagnosis of carcinoma of the cervical stump made in	108 (6.4%)
Patients treated with radium	99 (5.9%)
Probably genuine stump cases (diagnosed two years or more after operations)	57 (3.4%)

After satisfying this dictum in our present study, 57 probably genuine cases of carcinoma of the cervical stump remain, representing 3.4 per cent of our entire series of 1,676 carcinomas of the cervix (Table I).

The interval between the subtotal hysterectomy and the diagnosis of cancer of the retained cervix varied from two to twenty-nine years in this group of 57 cases; more than twenty years in 5 instances, and between ten and twenty years in 15 additional cases. Only 9 of the 57, or 15.8 per cent, had had the antecedent operation at The Mayo Clinic. The youngest of the 57 patients was thirty-four years of age, the oldest, sixty-four years, and the average age was 51.2 years.

A study of the fertility of the 57 patients yielded the results shown in Table II. The incidence of nonfertility (21.4 per cent) agrees with that reported by Branscomb[15] (20 per cent) and Meigs[18] (23 per cent) in studies of large series; 46 and 26 cases, respectively.

The antecedent operation, in more than half of the cases, was a subtotal hysterectomy for uterine myomas or for menorrhagia. An analysis of our own cases in relation to the incidence of the various causes of

Table II

INCIDENCE OF FERTILITY IN CASES OF CARCINOMA OF THE CERVICAL STUMP

Pregnancies	Patients	
	Number	Per cent
0	12	21.4
1	9	16.1
2	8	14.3
3	8	14.3
4	9	16.1
5	2	3.6
6	5	8.9
7	1	1.7
8	2	3.6
Total	56	100
No data	1	

antecedent operations is found in Table III. Thus, in all, 33 of the 57 patients had subtotal hysterectomy for uterine myomas or for menorrhagia, and 5 additional patients had that operation for pelvic inflammatory lesions. In 9 cases, malignancy may have been present.

The stage of the lesion, depicting anatomically the extent of involvement, is important in treatment and prognosis. Our 57 cases are classified according to our

Table III

INCIDENCE OF VARIOUS CAUSES OF ANTECEDENT OPERATIONS IN CASES OF CARCINOMA OF THE CERVICAL STUMP

Reason for operation	Cases in which antecedent operations were performed		
	Elsewhere	At The Mayo Clinic	Total cases
Uterine myomas	23	6	29
Menorrhagia	4	0	4
Inflammatory conditions	3	2	5
Suspected malignancy	8	1	9
Unknown	10	0	10
Total	48	9*	57

* Cases in which an antecedent operation was performed at the Mayo Clinic represented 15.8 per cent of the total number.

Table IV

CARCINOMA OF THE CERVICAL STUMP; STAGE OF LESION BEFORE TREATMENT

Stage	Cases	Per cent
I	0	0.0
II	11	19.3
III	30	52.6
IV	16	28.1
Total	57	100

previously published criteria for the treatment of cancer of the cervix. Briefly, in Stage I, cancer is limited to the cervix; in Stage II, there is extension beyond the cervix to the vaginal walls or into one or both parametria, without fixation; in Stage III, definite fixation exists through one or both parametria and in Stage IV the primary lesion is usually fixed and distant metastatic lesions often are present. The results of analysis of our series according to the findings at the time of the initial examination are given in Table IV.

Thus, we had a manifestly difficult group, with 80 per cent of the lesions representing advanced stages. Results of biopsies before treatment in the 57 cases are given in Table V. In the early years covered by this study, biopsies were not routinely performed. Hence, in 13 of these cases (22.8 per cent), biopsy was not per-

Table V

CARCINOMA OF THE CERVICAL STUMP; FINDINGS ON BIOPSY BEFORE TREATMENT

No biopsy (22.8%, early years)	13
Colloid carcinoma	1
Squamous cell epithelioma, not graded	3
Adenocarcinoma, not graded	3
Squamous cell epithelioma, Grade 2	6
Squamous cell epithelioma, Grade 3	16
Squamous cell epithelioma, Grade 4	10
Adenocarcinoma, Grade 1	2
Adenocarcinoma, Grade 2	1
Adenocarcinoma, Grade 4	1
Squamous cell epithelioma and adenocarcinoma, Grade 3	1
Total	57

formed; however, all were clinically malignant lesions, and 11 of the 13 patients died of cancer. It is interesting to note that of the 44 biopsies, 36 (82 per cent) revealed squamous cell epitheliomas; also, of the 37 graded specimens, 28 (75 per cent) were Grades 3 and 4, comparing favorably with the percentages calculated for the group of 1,676 cases.

Treatment of carcinoma of the cervical stump is a difficult problem. All of these lesions come under our "modified" group in classification of treatment of carcinoma of the cervix, as previous operation has ablated the fundus of the uterus and has imposed a limited form of treatment. Results of radium therapy in stump cases vary greatly in the reports from different clinics. Von Graff,[5] in 1934, reviewed all of the literature and has found the rate of cure by irradiation or by operation and irradiation in 428 cases to be 9.3 per cent. Meigs[18] described treatment in 10 cases, with a rate of cure of 7.6 per cent for four years. Nuttall and Todd reported a series of 20 cases in which a five year cure was obtained in 50 per cent. In 31 cases in which treatment was given in George Gray Ward's service, Sackett[19] quoted results over a period of five years of survival in 48.4 per cent of cases. Healy and Arneson,[10] in treating 36 patients, obtained a five year cure in 14 per cent.

Dangers of treatment have been cited by many radiologists. Nuttall and Todd[17] have emphasized that, in their treatment, radium is never placed in the cervical canal, but is packed off from the rectum and bladder. Jeanneney[20] stated that care is necessary in applying radium because of the proximity of intestinal loops; Phaneuf[21] has warned of increased danger of vesicovaginal and rectovaginal fistulas after treatment because by ablation of the fundus uteri a heavy source of filtration is removed. Counseller and Foor[22] reported the closure of an enterovaginal fistula which developed in a cervical stump a year after radium treatment; he warned that a loop of bowel may be too closely adherent to the stump of the cervix.

Table VI

Carcinoma of the Cervical Stump; Duration of Life After Last Radiation Treatment

Duration of life	Patients	Per cent
Less than 1 year	13	22.8
Less than 2 years	14	24.6
From 2 to 5 years	15	26.3
From 5 to 10 years	9	26.3 { 15.8
More than 10 years*	6	26.3 { 10.5
Total	57	100.0

* Includes patients now living 19, 17, 16 and 12 years after treatment.

Treatment in our 57 cases carried out over a period of fifteen years, has shown alterations in our technique from time to time. Treatment was mainly with radium, followed with roentgen therapy. The majority of patients received one course of radium therapy, followed by two courses of roentgen therapy, about three months apart. One course of radium therapy, followed by roentgen therapy, was given in 24 cases, two courses a few months apart in 10 cases, three courses in 5 cases, and more than three courses in 8 cases. Seven patients had radium treatment only, and 3 had roentgen therapy only. Prior to 1920, radium treatment consisted of the introduction of highly filtered tubes of radium into the vagina and rectum. Since 1920, the treatment has consisted of three or four applications in the cervical canal and two or three vaginal treatments, totalling approximately 4,000 millicurie-hours over a period of about two weeks. Roentgen therapy consisted, up to 1923, of moderate voltage treatments, approximately 135 kv.; from 1923 to the present, high voltage has been used, approximately 200 kv., over four to six portals, with 0.75 mm. copper and 1 mm. aluminum filtration, at a distance of 50 cm., 560 r to the field. The results of treatment in the 57 cases are recorded in Table VI.

Hence, patients who live beyond the five year period, usually judged to be "cures," numbered 15, or 26.3 per cent of

TABLE VII

CARCINOMA OF THE CERVICAL STUMP; ANALYSIS OF THE 15 "CURED" CASES

Grade of lesion	Cases
No biopsy	2
Squamous cell epithelioma, Grade 4	3
Squamous cell epithelioma, Grade 3	6
Squamous cell epithelioma, Grade 2	1
Adenocarcinoma, Grade 2	1
Adenocarcinoma, Grade 1	1
Adenocarcinoma (ungraded)	1

the total number. Of the 15, five had died subsequently; one of a heart attack nine years after the last treatment, without evidence of recurrence of the malignancy, and one of pneumonia, eleven years after treatment, also without evidence of cancer. In the other 3 cases, data regarding the cause of death were not available. The results of analysis of these 15 so-called cured patients in regard to biopsy are given in Table VII. This distribution agrees closely with that of the total group of 57 cases. Of the 13 microscopic studies, 77 per cent revealed squamous cell epithelioma; of the graded lesions, 75 per cent were grades 3 and 4.

The distribution of the 15 "cured" cases, according to the stage of the disease, differed considerably from that of the total group. Eighty per cent of the 57 cases represented Stages III and IV, whereas, of our 15 "cured" cases only 60 per cent represented Stages III and IV (Table VIII).

TABLE VIII

CARCINOMA OF THE CERVICAL STUMP; DISTRIBUTION ACCORDING TO STAGES

Stage	Cases	Per cent
I	0	0
II	6	40
III	6	40
IV	3	20
Total	15*	100

* Five year cures according to stage before treatment:
54.55% of Stage II.
20.00% of Stage III.
18.75% of Stage IV.

We do not have time for description of individual cases, but one case is unusually interesting and merits mention. A patient, aged sixty-one, had had a hysterectomy for uterine myomas two years previously; we treated the patient in 1930 with radium and roentgen rays for squamous cell epithelioma of the cervical stump, Stage III, Grade 3. This lesion cleared up completely; but the patient returned in 1932; she then had adenocarcinoma of the rectum, Grade 2. This was treated with radium, and she has remained well and free of recurrence.

Let us now consider briefly the "coincident cases," the 42 cases in which the diagnosis of cancer was made a month to two years after removal of the uterus; with this brief interval we may assume carcinoma to have been present when the hysterectomy was performed. The patients in this group were younger than those in the group of cases in which true carcinoma of the stump was found; the average age in the former group was 43.8 years. In 17 cases, or 40 per cent, in which treatment was given in the early years, biopsy was not performed. Of the remainder, 87.5 per cent were cases of squamous cell epithelioma, and 79 per cent of the lesions were Grades 3 or 4. The stage of the disease was farther advanced than in the true stump cases; 93 per cent were in Stages III or IV (Table IX).

TABLE IX

CARCINOMA OF THE CERVICAL STUMP; "COINCIDENT" CASES DIAGNOSED LESS THAN TWO YEARS AFTER OPERATION

Stage	Cases	Per cent
I	0	0.0
II	3	7.1
III	21	50.0
IV	18	42.9
Total	42	100.0

The results of treatment were as listed in Table X. The results of treatment in these cases have not been so good as in the

true stump cases. Instead of 26.3 per cent of cures as in the true stump cases, we obtained 21.4 per cent of cures in this group; but whereas in the true stump cases 22.8 per cent of the patients died within the first year after treatment, in the "coincident" class, 54.8 per cent died within the first year. As Nuttall and Todd[17] pointed out, we expect a poor result in the "coincident cases," a result comparable to incomplete surgical excision of a carcinomatous lesion anywhere in the body.

One patient in this "coincident group" is of special interest. In 1929, she had had a "chemical hysterectomy" at The Mayo Clinic for menorrhagia (the only case of this type of operation included). One and a half years later she returned, and was found to have advanced carcinoma of the cervix, squamous cell epithelioma, Grade 4. This was treated with one course of radium and two courses of high voltage roentgen therapy in the autumn of 1930. The carcinoma disappeared and she remained well and free of symptoms until the autumn of 1937, seven years later, when an extensive recurrence (or a new malignant lesion) appeared in the cervix. A limited palliative radium treatment was given but she died of carcinoma in August, 1938.

Another important feature in this study should be an attempt to gauge whether better results have attended our changes of technique throughout the years (Table XI). Of the 57 cases of carcinoma of the cervical stump, in 14 treatment was given in the first five years, 1915 to 1919 inclusive. Of these, 2 died within the first year, and there were 4 "cures"; that is, the patients remained in good health for more than five years. From 1920 to 1924, inclusive, 17 patients received treatment; 4 died in the first year and 3 were cured. From 1925 to 1930, inclusive, of 26 patients treated, 7 died in the first year, but 8 were cured. Thus, of 15 cured patients, only 4 were treated between 1915 and 1919, inclusive, and more than half were treated in the span from 1925 to 1930. The 42 "coincident" cases show a greater difference. In the years 1915 to 1919, inclusive, 10 patients were treated and all died within the first year. From 1920 to 1924, inclusive, 12 received treatment and 4 died within the first year, but 2 patients were curde. In the final group, from 1925 to 1930, inclusive, of 20 patients treated, 9 died in the first year, but 7 cures were obtained. Thus, of the 9 cures, not one was obtained in the first five year span, 2 were obtained in the second, and 7 in the third.

TABLE X

CARCINOMA OF THE CERVICAL STUMP; "COINCIDENT" CASES, LENGTH OF LIFE AFTER TREATMENT

Duration of life	Patients	Per cent
Less than 1 year	23	54.8
Less than 2 years	6	14.3
From 2 to 5 years	4	9.5
From 5 to 10 years	5	21.4 { 11.9
More than 10 years*	4	21.4 { 9.5
Total	42	100.0

* Includes patients living 14 and 13 years after treatment.

TABLE XI

CARCINOMA OF THE CERVICAL STUMP
(57 cases)

Period	No. treated	Cured	Died in 1st year
1915–1919	14	4	2
1920–1924	17	3	4
1925–1930	26	8	7
"Coincident" cases (42 cases)			
1915–1919	10	0	10
1920–1924	12	2	4
1925–1930	20	7	9

CONCLUSIONS

Carcinoma of the retained cervix, subsequent to a supravaginal hysterectomy, is a very serious condition. When discovered, most of the lesions are in advanced stages, and the prognosis is poor. This condition occurs at the time of the menopause, or slightly later, and occurs most

often after a subtotal hysterectomy for uterine fibromyomas. Undoubtedly, as Branscomb[15] has suggested, when uterine myomas are known to be present in cases of vaginal bleeding, investigation of possible causes of vaginal bleeding other than uterine myomas may not be considered, and a coincidental cancer of the cervix may be easily overlooked.

For the surgeon who must decide between performing a subtotal hysterectomy and a panhysterectomy when removal of the uterus is necessary, acquaintance with the true incidence of cancer in the cervical stump is of vital importance. Unfortunately, this information is difficult to obtain. The follow-up of cases by surgical clinics yields a very low incidence, which is natural when we remember that patients may have to be traced for two or three decades. Radiologic clinics, in the treatment of carcinoma of the cervix, have found a far higher incidence of malignancy in the retained stump than have surgical clinics.

In our experience, among 1,676 patients who had carcinoma of the cervix treated with radium at the Mayo Clinic from 1915 to 1930 inclusive, 108 were diagnosed as carcinoma of the cervical stump. By eliminating a few patients who were not treated here, or who received treatment by cauterization only, 99 cases remain, 6.4 per cent. However, further pruning was necessary. We agree with Nuttall and Todd,[17] and with Sharples,[16] that if two years or longer have elapsed between subtotal hysterectomy and the discovery of the malignant lesion in the retained cervix, the lesion is probably a true carcinoma of the cervical stump, and not a "coincident" or dual carcinoma which was present before the operation was performed.

On this basis, we had 57 cases remaining, or 3.4 per cent of the total series. The interval between operation and the diagnosis of malignancy was more than twenty years in 5 cases, and between ten and twenty years in 15 additional cases.

We found, on analysis, that careful radium and roentgen therapy does yield worth-while results, which have been improving with changes in technique. Cure for more than five years was obtained in 26.3 per cent of the cases. These patients are now living and well nineteen, seventeen, sixteen and twelve years, respectively, after their last treatment, although the extent of the lesion on diagnosis had represented an advanced stage (80 per cent were in Stages III or IV) and the grade of the cancer was high in cases in which biopsies had been taken (75 per cent were Grades 3 or 4). Incidentally, patients who have never been pregnant are not immune to cancer of the cervix. In 21 per cent of cases in our series a history of nonfertility was obtained.

Results were not so fortunate in the "coincident" cases, or dual malignant lesions, those discovered less than two years after operation with carcinoma probably coexisting at the time of the operation. As Nuttall and Todd[17] had emphasized, results in these are comparable to the results of incomplete operation for a malignant lesion anywhere in the body. Although the five year survivals in our series were only 5 per cent less (21.4 per cent), more than half of the members of the group died within the first year after treatment (54.8 per cent), contrasted with 22.8 per cent of the true carcinomas of the stump. The lesions were more advanced when first seen; only 7 per cent were in Stage II, contrasting with the true stump group in which 20 per cent were in Stage II.

Hence, although in the presence of carcinoma of the cervical stump careful irradiation can accomplish much and the prognosis is not utterly bad, much remains to be accomplished in the way of prevention. The seriousness of carcinoma of the cervical stump must be publicized and reemphasized. Whenever a subtotal hysterectomy is performed, a conscientious examination of the cervix should be a requisite. After such an operation, the patient should have pelvic examinations at stated intervals, and should be instructed

to come voluntarily for attention at any time, if vaginal bleeding occurs.*

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* For discussion see page 571.

IRRADIATION OF CARCINOMA OF THE CERVIX UTERI IN PREGNANCY*

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SINCE 1909 when Williams published the results of his experiences together with a summary of the literature on the treatment of carcinoma of the cervix uteri during pregnancy, irradiation has become a factor. This review is intended to investigate what progress, if any, modern surgery has made and what radium and roentgen radiation have added to the treatment.

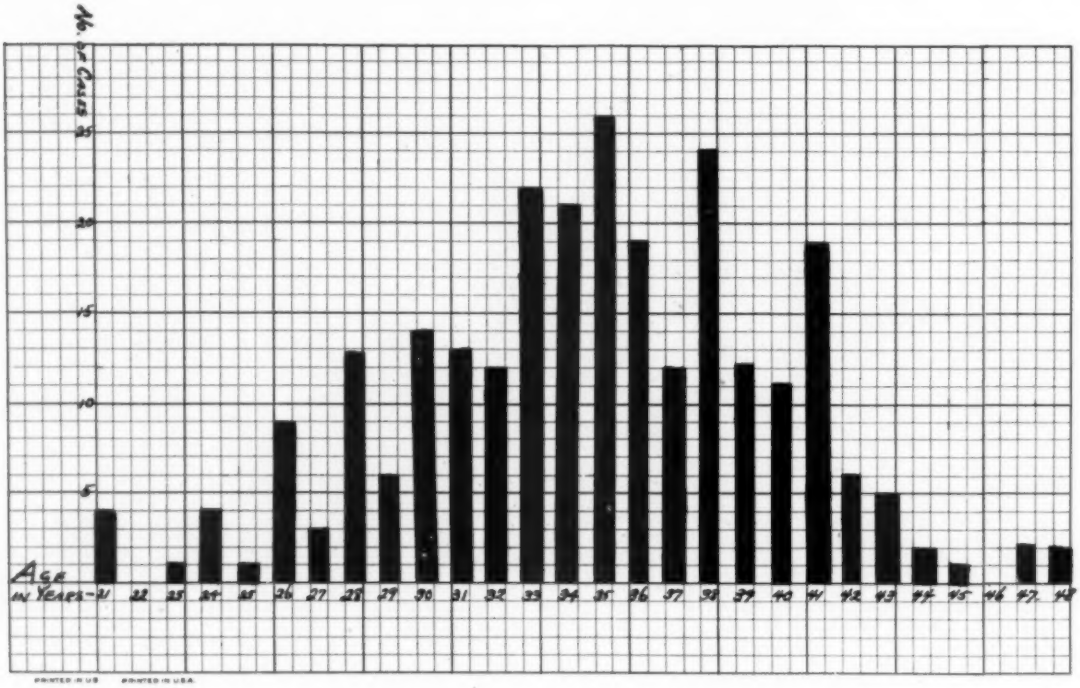

Chart I

Most authorities agree today that carcinoma of the cervix is treated as well if not better by irradiation than by surgery in most instances. The question whether the concomitant pregnancy changes this dictum remains to be answered by the results of experience. It is obvious that this lesion has to be considered from two points of view—surgery and obstetrics. The latter has two considerations—the mother and the child.

It is a well known fact that cancer of the cervix most commonly occurs after the age of fifty when pregnancy is exceedingly rare. Therefore, in dealing with cases of pregnancy complicated with cancer we usually deal with a younger group of patients. The oldest person in this series was forty-eight and the youngest was twenty-one, at which age there were four. Of 264 cases where the age was mentioned 175, or 66 per cent, were in the fourth decade (Chart 1).

The incidence of cervical carcinoma among pregnant women varies from the figures of Mussey 1 in 437, to 1 in 12,383 given by Hirst. It is quite evident that

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very few doctors not connected with a large obstetrical clinic see the two conditions in association, yet it is important to watch for that one case so that it may be properly treated.

This report is based on 280 cases published between 1895 and 1936 inclusive, adding one unpublished case treated by Pomeroy, and two by the author one of which is mentioned in the monograph by Bubis.

test, or diagnosed by biopsy and which is discovered in the latter half of pregnancy may be said to have originated after conception. On the other hand, a growth involving the whole cervix or inoperable in the first half of pregnancy undoubtedly preceded conception.

But to judge the age of the cancer by its extent calls forth the age old discussion of the effect of pregnancy on the rate of the growth of the cancer. Zweifel's classic clini-

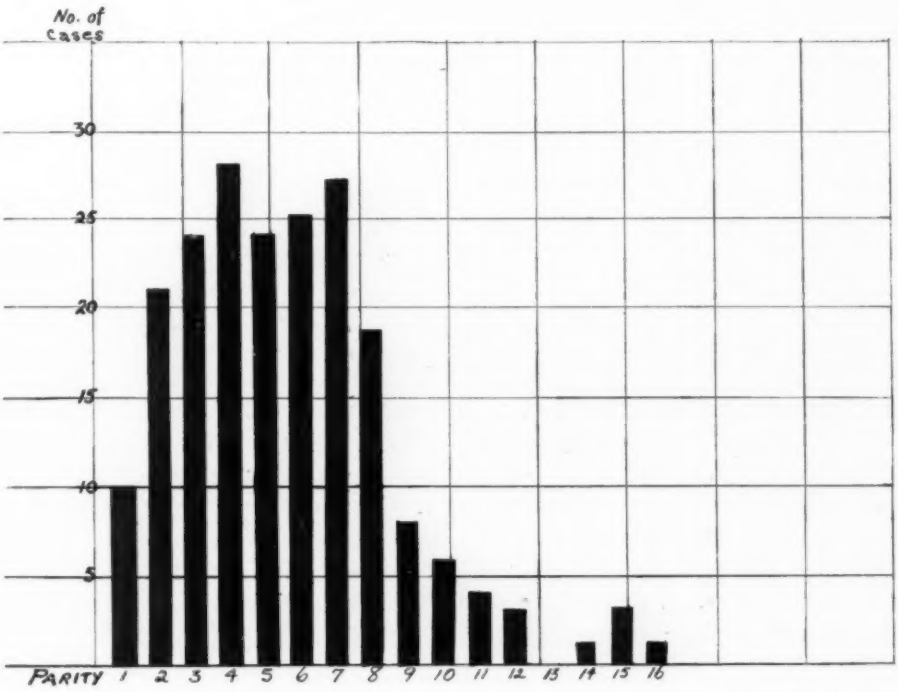

Chart II

Pregnancy does not tend to develop an immunity to carcinoma as shown by the fact that there was an average of over 5.4 pregnancies per patient in my series. Only ten were primiparas and 21 were para II whereas 159 were para III to para X (Chart II).

In all cases it is a question as to which precedes, the pregnancy or the cancer. The decision in each case must rest in great part on the extent of the growth and the month of pregnancy. For example, a small malignant polyp or bleeding ulcer on one lip which might be suspected from the Lugol's

cal experiment is often cited as evidence that pregnancy hastens the rate of growth. He marked the edge of a carcinoma of the cervix with a thread and found it extended two finger breadths in fourteen days. Ewing said, "Pregnancy has an unfavorable influence on the course of many uterine carcinomas not always apparent."

This seems to be borne out in one of my cases. She was treated with radium to the cervix and later a panhysterectomy was performed. There was no malignancy discoverable in the specimen and yet twelve months later the patient returned with in-

volvement of the pelvic nodes as proved by laparotomy. Thus it had spread rapidly during pregnancy and extended beyond the uterus. One of Sommer's cases was a woman, aged thirty-six, who was examined for pelvic pain in the eighth month. Nothing pathological was found. At term the growth was inoperable.

On the other hand, Siebold observed a spontaneous cure of genital carcinoma owing to a supervening pregnancy. Varniew in 1897 reported a case presenting an enormous carcinoma of the portio in a gravid woman. The following year another pregnancy occurred and death did not take place until October, 1900. Again there are case reports of second pregnancies after treating the cancer during the gravid state. Vitanza in 1898 did a high cervical amputation for carcinoma of the cervix during pregnancy. The patient was delivered later after forcible dilatation of the cervix and two years later was delivered again at eight months by a midwife. Vitanza found her free of cancer two years after that. His next case was operated on similarly in the third month. She was delivered at term of a 3,500 gram baby and of another two years later. In 1920 Siredey treated a pregnant woman for cancer of the cervix with radium. She aborted six months later. Two years after that she was again pregnant. The cervix remained clear and Siredey preformed a cesarean at term.

Because of a possibility that a pregnant woman has some cancer resisting hormone or hormone reaction I administered to some advanced carcinoma patients large doses of prolan and others I transfused with blood from pregnant women. Both groups of patients had severe reactions characterized by nausea, vomiting and mild to moderate shock, leading us to conclude that there may be some substance called forth in the body by pregnancy to resist tissue invasion (cancer).

Carcinoma has its effect on pregnancy. The inanition from cancer results in retarding the growth of the child. It may be a source of hemorrhage or infection. By spread of infection or of neoplasm it increases the proportion of abortions. It may make the cervix rigid and obstruct delivery or make it friable and lead to rupture and death.

Symptoms. A patient usually pays no attention to a leukorrhea even after it becomes foul unless it is bloody. Thus sometimes she will miss what may be the first symptom of cancer. After a few months of amenorrhea a woman who realizes she is pregnant for the fifth or sixth time will go to her doctor at the first sign of bleeding from the vagina. Bleeding, therefore, is the most prominent and most common symptom and is usually heeded at once by the pregnant woman. The doctor thinking of the most common occurrence will treat her for a threatened abortion either with or without examining her. When we recall the fact that a carcinoma of the cervix occurs only once in 1,500 to 10,00 pregnancies we can see that he will rarely be wrong. But in that one case he may put the patient to bed to await developments. He will in this way lose weeks unless the hemorrhages become so profuse that he will examine the cervix both manually and visually. Then he will discover usually a growth which may need a biopsy to determine its nature. It is this type of cancer which gives a favorable prognosis today if operated on in that stage.

If the hemorrhage occurs in the late months of pregnancy, placenta praevia is the first diagnosis to come to the mind of the obstetrician. Cases are on record in which cesarean sections were done because of this diagnosis unaware of the carcinoma of the cervix which was found only after the operation.

On the other hand, a woman may have a carcinoma of the cervix and bleed irregularly so that she has lost track of the menses. She will not realize that she actually has an amenorrhea and that the bleeding is due to a growth. Not realizing that she is pregnant, she will tell her doctor she has not missed a period. The doctor will

find the carcinoma of the cervix and diagnose the enlargement of the womb as part of the growth. The result will be that the pregnancy will not be discovered until irradiation is given. If, however, the dictum is followed, that irradiation should be preceded by curettage as is done with radium there would be no question of a child injured by irradiation in such cases. In 1909 Williams wrote that pregnancy could not be diagnosed in some cases. Today we have the Friedman test which will prevent our overlooking a pregnancy if use is made of it.

In 1881 Thomas Spencer Wells reported the first successful hysterectomy by Freund's technique for carcinoma of the cervix in the gravid uterus. Thereupon Billroth, who had performed two vaginal hysterectomies for the same condition, wrote Wells: "Of what use are all our pains and art?" Wells answered: "May we not hopefully reply that if not invoked too late success may reward our pains and art." With improved surgical technique and earlier consultations in this group of patients an increased operability has been noted. Schweitzer found 9 operable out of 11 cases and obtained 5 five year cures among these 9. Weibel operated on 24 out of 26 cases.

Table 1 reveals the expected, namely that maternal mortality increases directly with the birth rate. This must be a warning, then, not to delay operation in order to obtain a living child. It may be pointed out that radical hysterectomy in expert hands has very little greater mortality than panhysterectomy before the seventh month and that one series of 11 cesarean sections followed by the Wertheim operation showed only one maternal death. This may be interpreted to favor the theory that pregnancy holds the cancer in check. The release of this check may be assumed by the maternal mortality of 63 per cent in post partum vaginal hysterectomies as compared with 35 per cent when vaginal hysterectomy was done early in pregnancy.

Table I

	Total	Mothers Lived	Mortality per cent	Child Lived	Birth Rate per cent
Cesarean section	10	0	100	6	60
Cesarean section and abdominal hysterectomy	17	7	59	9	52
Cesarean section and supracervical hysterectomy	10	1	90	4	40
Cesarean section and Wertheim operation	11	10	9	4	36
Cesarean section and vaginal hysterectomy	2	1	50	1	50
Total cesarean sections	50	19	60	24	48
Wertheim operation	42	26	38	1	
Abdominal hysterectomy before 7 mo.	34	23	32		
Abdominal hysterectomy after 7 mo.	2	0	100	1	
Vaginal hysterectomy	14	9	35	3	21
Vaginal hysterectomy post partum	11	4	63	4	36
Vaginal cesarean section and vaginal hysterectomy	4	2	50	2	50
Vaginal delivery	31	5	83	22	71
Cervical amputation	3	3	0	3	
Not classified	1	0	0		

Thirty-two patients were treated by irradiation alone (Table II). Fourteen mothers and 11 children lived, a maternal mortality and birth rate of 56 per cent and 37 per cent respectively. Besides 10 abortions or miscarriages in this group there were 2 microcephalics. One must consider these two failures.

Postconception irradiation before the seventh month as a cause of microcephaly has been confirmed by Goldstein and Murphy who investigated 106 women so treated. These women gave birth to 74

TABLE II

	Before Seventh Month					After Seventh Month					Totals All Months				
	Total	Mother Lived	Maternal Mortality per cent	Child Lived	Birth Rate per cent	Total	Mother Lived	Maternal Mortality per cent	Child Lived	Birth Rate per cent	Totals	Mother Lived	Maternal Mortality per cent	Child Lived	Birth Rate per cent
Irradiation ante partum or pre-operative	19	8	57	6	31	7	1	85	6	85	26	9	65	12	
Irradiation post partum or post-operative	14	8	35	1	7	23	10	56	16	69	37	18	51	17	
Irradiation ante and post partum or pre- and post operative	18	8	55	11	60	5	1	80	2	40	23	9	60	13	
Months not given											5	3	40	3	
Totals	56	24	57	18	32	35	12	65	24	64	91	39	57	45	49.5
Irradiation alone from above groups	26	11	60	9	34	6	3	50	2	30	32	14	59	11	37

TABLE III

	Cases	Maternal Results			Child Results		Vaginal Births	Miscarriage and Abortions	
		Lived	Died	Mortality per cent	Lived	Died			
Irradiation alone	32	14	18	59	12	37	14	10	2 microcephalics
Irradiation then cesarean section	8	3	5	68	7	86			
Cesarean section then irradiation	6	2	4	66	3	50			
Irradiation, cesarean section then irradiation	5	2	3	60	4	80			
Irradiation, cesarean section then hysterectomy	7	2	5	71	4	58			
Cesarean section, hysterectomy and irradiation	7	2	5	71	6	86			
Cesarean section, Wertheim operation and irradiation	4	2	2	50	3	75			
Irradiation, cesarean section, hysterectomy and irradiation	2	0	2	100	0				
Irradiation and hysterectomy	2	0	2	100	1	50	1		
Hysterectomy then irradiation	9	6	3	33	2	22			
Irradiation, hysterectomy, then irradiation	1	1		0	1				
Irradiation then Wertheim operation	2	2		0	1		1		
Wertheim operation then irradiation	5	4	1	20	1		1		
Irradiation, Wertheim operation then irradiation	1	1		0	0				

full term children, 38 of these children showed disturbances of anatomy or of function. Sixteen of these 38 were microcephalics and 2 others were mentally deficient without microcephaly.

Although many children have been reported normal in this series, one cannot be sure because they were reported soon after birth and microcephaly may not be recognized until the child is four years of age. Zimmermann reported such a child apparently normal until seven years old. This, then, together with the poor results are arguments against irradiation alone for cancer of the cervix during pregnancy.

Irradiation in combination with surgery follows the same rules as far as results go (Table III). When irradiation supplemented cesarean section alone or cesarean and hysterectomy it did not improve the results. When used with total hysterectomy or the Wertheim operation in the early months, the maternal mortality was 33 per cent and 20 per cent respectively—apparently a slight improvement over the operative treatment without irradiation only with the Wertheim operation.

The 2 cases that I have to present bring out some of the indications and objections to various forms of treatment.

REPORT OF CASES

Case I. An Italian woman, aged thirty-eight, was admitted to Mt. Sinai Hospital (under the care of Dr. Lesinger) on January 29, 1926. She was five months pregnant and para v. Onset ten days before admission with pains simulating labor pains. She said the "bag of water broke." Five days after this she noticed bleeding, scant at first but becoming more profuse each day. Examination revealed a uterus extending to the umbilicus. The movements of the child were felt. By rectal examination an irregular mass was felt protruding from the cervix. This was then confirmed by vaginal examination. The doctor stated that he thought it was a hand that protruded. She slept most of the night under ¼ grain of morphine. She passed large clots of blood the next morning and by evening was bleeding profusely. She was then given 1 cc. of pituitrin. Bleeding became less. Because she had no pains she was discharged on the fourth day with a diagnosis of "threatened abortion."

Ten days later she was readmitted because of severe bleeding. The same protruding mass was again felt. This time the cervix was visualized with a speculum and a polypous bleeding growth was seen. No fetal parts presented. This was diagnosed indurated cervical polyp and removed next day when it proved to be an epidermoid carcinoma. I was then consulted. I thought, inasmuch as it was a polypous growth, that I might hold it in check for two months, with radium treatment when the child could be removed by cesarean section. This was done. Radium therapy, 3,000 mg-hr., was given to the cervical canal. On April 20, 1926, Dr. Bubis did the cesarean section and immediate panhysterectomy and transfusion. The child died soon afterwards. No enlarged nodes were found in the pelvis. Dr. Kline reported that after careful examination and the taking of many sections there was no tumor tissue in the uterus or adnexa. There was an area of necrosis 3 mm. in diameter which was where the radium had been most effective. The patient made an uneventful recovery. She was discharged on the eighteenth postoperative day. She was then given roentgen therapy to the pelvis by Dr. H. Mahrer. His method consisted of treating four fields 15×15 cm. each, with 200 kv., 4 ma., for thirty minutes at 35 cm. distance, using a filter of 0.5 mm. copper and 1.0 mm. aluminum. The patient gained 30 pounds in the course of the ensuing year. She was readmitted to the hospital April 1, 1927. Five weeks previous to this admission she complained of pain in the back and right flank. She lost 8 pounds in five weeks. Dr. Bubis again did a laparotomy only to find a chain of hard nodes along the iliac vessels on each side. Dr. Kline reported metastatic carcinoma in lymph nodes.

This patient died in 1928, a little over two years after the onset of the carcinoma.

In retrospect we must appreciate that it must be usual to believe bleeding at the fifth month of pregnancy is due to threatened abortion from which carcinoma cannot be diagnosed without visualization and sometimes biopsy. We realize, too, that it is the practice of obstetricians to examine a pregnant woman as little as possible to avoid infection. Thirdly this is a striking instance of the ability of radium to destroy

the local growth and fail to destroy the growth already in the lymphatics. Therefore, it seems that just as the Wertheim operation has failed to cure those patients in whom the iliac nodes are involved, so, too, radium is suited for growths that are confined to the uterus. Fourthly, one must naturally raise the question—did the two months waiting for the child to become viable give opportunity for extension of the growth to the lymphatics, and would the patient have been cured if hysterectomy had been done as soon as the diagnosis was made? I feared more irradiation previous to cesarean section because of the irradiation effect on the child. I should be inclined under similar circumstances to act differently now. I would disregard the child and if preoperative radium treatment were given at all, operate two weeks later.

Case II. A Polish woman, aged forty-two, para VIII, entered Mt. Sinai Hospital on Dr. Garber's service July 31, 1927. She was six months pregnant. Her seventh child had been born two years previously. She complained of bleeding for four months and abdominal pain since the afternoon preceding admission. She was anemic; red blood count 3,000,000, hemoglobin 60 per cent. Vaginal examination revealed an indurated papillomatous mass protruding from the cervix. Biopsy confirmed the diagnosis of epidermoid carcinoma. On August 3, a stillborn child was delivered by cesarean section. The pelvis was free of growth. This was followed five days later by heavy roentgen irradiation, as in the former case, and she was referred to me for the first time on August 22 for radium therapy. The growth occupying the cervix was 1½ inches in diameter. I applied 100 mg. in the cervical canal for twenty-four hours; October 28, 1927, 2,000 mg-hr. more. On July 23, 1928, the uterus was free but the mass was palpable high in pelvis. More roentgen irradiation given by Dr. Mahrer. The patient died early in 1929, a little less than two years after the onset.

From the history of this patient and the fact that she was not a very observing woman, it is fair to suppose that she had failed to take notice of a vaginal discharge before conception and that the bleeding in the second month was from a carcinoma of more than two months' duration. Therefore, this was a preconception malignancy and well advanced after six months of pregnancy as evidenced by abdominal pain. It was a failure for irradiation.

Therefore, I believe we can formulate the treatment of carcinoma of the cervix depending on the stage of pregnancy as well as on the extent of the growth.

First: If the growth is operable and the child inviable, there is only the mother to consider. Delay may mean that the growth will advance from an operable to an inoperable one. It will diminish the chance of cure for the mother. As the carcinoma advances the chance of the child for life diminishes. Therefore, it is folly to wait for the child to become viable. Preoperative irradiation with radium must be incomplete as the uterine cavity cannot be irradiated thoroughly. Extensive and complete roentgen irradiation may make operation difficult, as well as cause abortion through a diseased cervix, and also deformities, especially microcephaly. Therefore inasmuch as one's greatest problem is with the patient, the inviable child should be disregarded in the treatment. A Wertheim operation is favored because the tissue planes are easily dissectible. Irradiation to the point of early abortion should be considered only in case the surgeon is not capable of the Wertheim operation. Irradiation to the cervix and supracervical hysterectomy should be discouraged just as much as in the nongravid carcinoma. In view of the poor results that occurred in postpartum carcinoma I believe that to leave any growth after removal of the fetus will mean that the restraining influence (fetus) will be removed and that will invite disaster.

Second: If the growth is operable and the child viable we prefer cesarean section and a Wertheim operation or panhysterectomy at once followed by postoperative irradiation as soon as the patient's condition warrants. There is not much choice, however, between cesarean section and

TABLE IV

LIST OF CASES IRRADIATED

Name	Mo.	Radiation Therapy (ap=ante partum, pp=post partum)	Operative Procedure	Result on	
				Mother	Child
Cotte, G. 1928	8½	Radium, postoperative	Cesarean, total hysterectomy without removal of parametria	D.	D.
Döderlein, A. 1928	7	110 mg. radium bromide intravaginally for 24 hr. (ap)		D.	L.
Field, C. E. 1922	?	Radium: (1) 100 mg. within cervix; screen, 1 mm. gold and brass; 0.5 mm. rubber, 8 hr. crossfiring from a sacral pad containing 300 mg. screened with 1.5 cm. felt 1.5 mm. rubber and 0.5 mm. metal 16 hr.; (2) postcervical bomb 140 mg. screened with 1.5 mm. brass and 1.5 mm. hard rubber 8 hr.; (3) 100 mg. standard screen within cervix. Total radiation, 7320 mg-hr. (ap)		D.	L.
Hauch, E. 1927	8–9	Preoperative: radium; 3 tubes inserted total 125 mc-hr. with aluminum filter, rectum protected by lead sheet 2 mm. thick	Cesarean section	D.	L.
Same 1927	9	Radium: 3 tubes, 22 hr. 11 exposures x-ray. Radium amounts not given (pp)		D.	?
Same 1927	?	Postoperative: 21st day; 2 tubes radium for 20 hr. X-ray at 5½ weeks, radium at 8 weeks. Amounts not given	Cesarean section	L.	?
Laquerriere, and Labelle	6	X-ray, 39 treatments, externally 2–8 min., then 13 cervical and 14 external. After delivery, 20 more treatments. No dosage amounts given (ap and pp)		D.	L.
McGlinn, J. A. 1927	3	2400 mg-hr. radium by capsule and needles into cervix (pp)	Aborted before treatment	D.	D.
Same 1927	9	3600 mg-hr. X-ray 10 mo. later (ap and pp)	Cesarean section	D.	D.
Mundell, J. 1927	3	2100 mg-hr. radium repeated in 2 mo. (ap)	Aborted	D.	D.
Schilling, N. 1924	4½	Preoperative; local radium 100 mg. for 24 hr.	Cesarean section after 18 hr. labor; panhysterectomy	D.	D.
Gill, J. J. 1926	5	Postoperative; deep x-ray therapy	Hysterectomy and appendectomy	L.	D.
Vital, Aza 1917	6	Radium therapy over a period of 3 mo., 12,500 mg-hr.—50 mc-destroyed (ap)	Cesarean at term because of rigidity of cervix		L.
Strauss, A. Treated 1926	5	3000 mg-hr. radium intracervical (ap); postoperative x-ray therapy to pelvis, 200 kv. 4 ma. fiter 0.5 mm. Cu, 1 mm. (ap), 4 fields, 35 cm. distance	2 months later, cesarean section and immediate panhysterectomy; transfusion	D.	D.
Strauss, A. Treated 1927	6	Postoperative: heavy x-ray irradiation; 100 mg. radium, cervical canal, 24 hr. One month later, 2000 mg-hr.; 9 months later, mass palpable high in pelvis, roentgen irradiation given as in previous case	Stillborn child delivered by cesarean section	D.	D.

TABLE IV—(*Continued*)

Name	Mo.	Radiation Therapy (ap = ante partum; pp = post partum)	Operative Procedure	Result on	
				Mother	Child
Audelbert and Galy 1928	9	Post partum: Nov. 19, 1925 (6 weeks) 10 needles 2 mg., 21.60 mc-destroyed Nov. 28 and Dec. 2 x-ray. Dec. 3, 8–36 mc-destroyed.		L.	L.
Roy 1926–28	9	Post partum: radium 167 mc-destroyed in 7 days	At term. Cesarean section. Subtotal hysterectomy	L.	L.
Roy 1926–28	4	At 4 months: 47 mc-destroyed in 5 days. At 6 months: 3.4 mc-destroyed in 2 days. Post partum: 1 month later 17 mc-destroyed in 3 days	Difficult forceps delivery; premature	D.	D.
Roy 1926–28	7	Radium 27 mc-destroyed in 5 days (ap)	Cesarean section at term and subtotal hysterectomy	D.	L.
Roy 1926–28	7	Radium 47 mc-destroyed in 5 days Radium 12 mc-destroyed in 5 days (ap)	Cesarean section and subtotal hysterectomy	L.	L.
Karg-Carl 1928	6	Radium 3 times: Total 4000 mg-hr. Each about 1 month apart. Post partum further irradiation	Normal birth	D.	L.
Karg-Carl 1928	8	1320 mg-hr. in April (ap). Post partum irradiated twice	Normal birth June, 1925	L.	L.
Condamin, R. 1928	2	125 mg. 48 hr. Radium bromide (ap)		D.	D.
Condamin, Voron and Molin	5	125 mg. 48 hr., Jan. 9 and Feb. 1, 3 weeks post partum, 125 mg. 48 hr. (ap and pp)	March 25 (somewhat premature) delivered by vagina	L.	D.
Neill, Wm. 1935	7½	Dec. 15, 1926–4 glass radon capsules, 2.5 mc. implanted permanently in cervical stump. Dec. 18—1765 mc-hr. radon topically (ap)	Cesarean section; April, 1927, removed superficial metastatic nodule 1 cm. from right vaginal orfice with cautery	D.	L.
Neill, Wm. Jr. 1935	5	Topical application 3109 mc-hr. 10 months later, x-ray for a total of one S.E.D. over front and back of pelvis to establish artificial menopause (ap and pp)	Cesarean section	L.	L.
Neill, Wm. Jr. 1935	3	Topical application against cervix, 3600 mg-hr. in August, 1931 (ap)	Cesarean section in February, 1932	L.	L.
Neill, Wm. Jr. 1935	9	6 weeks postoperative: Topical application to cervix of 3000 mc-hr. and a series of deep x-ray. No change in 2 mo. Then 1 gold radon cap. 13.6 cm. permanently in cervix. 2 months later, 1000 mc-hr. against cervix	Cesarean section, June, 1931	D.	L.
Neill, Wm. Jr. 1935	1½ hrs. after diagnosis and birth	1½ years postoperative palliative x-ray. 1 week later 3000 mc-hr. radium irradiation	Cesarean section and supracervical hysterectomy	D.	L.

TABLE IV—(*Continued*)

Name	Mo.	Radiation Therapy (ap = ante partum, pp = post partum)	Operative Procedure	Result on	
				Mother	Child
Neill, Wm. Jr. 1935	5	Oct. 1930 large mass removed-dull spoon curette. Topical application radium 3000 mc-hr. June, 1931, 1000 mc-hr. in vaginal vault for recurrent ulcer. Dec. 1933—1440 mc-hr.—recurrence (pp)	Spontaneous delivery August, 1930	D.	D.
Weibel, W. 1928	5	Artificial abortion with radium (ap)		L.	D.
Weibel, W. 1928	9	Radium (ap)	No operation	D.	?
Shoemaker, G. E. 1920	9	Postoperative radium	Removal of cancerous area with cautery and scissors, then forceps delivery and packing with iodoform gauze	D.	D.
Kaplan, I. I. 1930	3	3 doses of high voltage—50 per cent of a skin erythema dose on anterior, 25 per cent on posterior pelvis. Post partum: "Colpostat" 45 mg. radium against cervix:—4300 mg-hr. over 4 days. 2 days later radium sound—30 mg. into uterus, 2880 mg-hr. over 2 days. Transfusion and high voltage x-ray to spleen—following 4 weeks more, transfusions (ap and pp)		L.	D.
Morris, S. W. 1935	6	2115 mg-hr. radium to cervix (ap)	3 days later, removal of uterus, tubes and ovaries	D.	D.
Morris, S. W. 1935	3	Postoperative 12 days, 2000 mc-hr. radon to top of vagina (pp)	Panhysterectomy under spinal anesthesia	L.	D.
King, Gordon 1935	9	Radium—14 days postoperative 4230 mg-hr. to cervix (pp)	Cesarean section and resection upper part of uterus	D.	L.
King, Gordon 1935	7	Radium—12 days postoperative. Repeated twice per vagina: 4320 mg-hr. (pp)	Supravaginal hysterectomy	D.	D.
Mussey, Report of Mayo Clinic 1923	4	Radium and x-ray, postoperative	Total hysterectomy	D.	D.
Mussey, Report of Mayo Clinic 1923	3	Radium, postoperative	Total hysterectomy	D.	D.
Mussey, Report of Mayo Clinic 1923	4	Radium and x-ray (ap)		D.	D.
Nevinney, H. 1931	9	Postoperative: secondary roentgen irradiation	Cesarean section followed by Freund-Wertheim; sacral anesthesia, tutocain solution	D.	L.
Cothala and Merat 1923	6	Radium refused for 1 month. Then 77 mg. radium bromide 24 hr. no reaction: 2 more hemorrhages 24 and 28 hr. later. Profuse discharge amniotic fluid (ap)	Cesarean section and total hysterectomy	D.	D.

TABLE IV—(*Continued*)

Name	Mo.	Radiation Therapy (ap = ante partum; pp = post partum)	Operative Procedure	Result on	
				Mother	Child
Brouha, M. and Gosselin, O. 1934	7	Radium: Tampons in posterior cul-de-sac, 13.33 mg. radium bromide in front of cervix filtered through 0.5 mm. platinum, 1.25 mm. gold, 10 mm. rubber, 12 thicknesses gauze 4 days. 19.2 mc-destroyed; 15 days later condition same, 28.8 mc-destroyed in 8 days. Postoperative x-ray 1800 r in 30 treatments	Cesarean section 14 days later, followed by total hysterectomy	D.	D.
Brouha, M. and Gosselin, O. 1934	5	Same as above except radium in cervical canal and in posterior and lateral cul-de-sac. Cervix dilated and miscarriage (ap and pp)	Hysterectomy and deep x-ray therapy	L.	D.
Masson, J. C. 1930	7	Malignant growth treated with radium postoperative	Porro cesarean section one month after first seen	D.	L.
Behney, C. A. 1930 (Keene)	6	Cautery amputation of cervix, 100 mg. radium 36 hr.: 2 months later delivered of apparently normal child. Then 100 mg. 36 hr. more	Child a microcephalic	L.	L.
Keene, F. E.	3½–4	2 weeks postoperative: wide cauterization of cervix, 2400 mg-hr. radium	Supravaginal hysterectomy and bilateral salpingo-oöphorectomy as a primary procedure	L.	D.
De Nabias 1925	8	Postoperative: 4 tubes radium in cervix—each 10 mg. filtered through 1 mm. platinum for 5 days. Then 3 tubes through vagina. 7200 mg-hr. or 54.60 mc-destroyed	Median laparotomy—difficult to exterorize uterus—living child. Round and tubo-ovarian ligaments sectioned. Uterine arteries ligated; cervix sectioned	L.	L.
De Nabias 1925	4	4 applications: 4320 mg-hr. or 32 mc-destroyed. Postoperative 54 mc-destroyed in 12 days (ap)	Cesarean section at 8½ months followed by subtotal hysterectomy	L.	L.
Zimmermann, R. 1928	6	Post partum mesothorium and x-ray	Spontaneous miscarriage through growth	D.	D.
Zimmermann, R. 1928	6	Mesothorium intracervical 100 mg. Intravaginal 50 mg. for 24 hours—3600 mg-hr. Postoperative x-ray. Also 100 mg. mesothorium intravaginally	Total hysterectomy, cesarean section at 7 mo.	D.	?
Zimmermann, R. 1928	7	109.6 mg. mesothorium 24 hr. in crater. Post partum roentgen irradiation (ap and pp)	Miscarriage at 8 months	L.	D.
Zimmermann, R. 1920	5	Mesothorium 3 times at 6 week intervals, twice 100 mg. intracervical and 50 mg. intravaginal for 24 hr.—3 times, total 4390 mg-hr. 12 weeks post partum: 109.6 mg. 24 hr. mesothorium	Normal delivery. Microcephalic	L.	L.
Paroli, G. 1935	3	Radium element—5760 mg-hr. in 3 weeks (ap)	Cesarean section	L.	L.
Siredey, and Gagey 1920 & 1924	8–10 weeks	Intracervical 15.7 mc-destroyed (ap)	Aborted 2 years later a cesarean section	L.	D. L.

TABLE IV—(*Continued*)

Name	Mo.	Radiation Therapy (ap = ante partum; pp = post partum)	Operative Procedure	Result on	
				Mother	Child
Hartmann, and Fabre 1924	4	11/24/22—cervical radium—25.92 mc-destroyed. 11/25/23—7.04 mc-destroyed (ap and pp)	3/11/23—cesarean section followed by supravaginal	D.	L.
Philipp, E. 1931	4	April 1924—118 mg. 30 hr. (in cervix, 1 tube 40 mg. and 1 of 26 mg. in front of cervix, 2 tubes 26 mg.). Repeated in 9 days. Total—7000 mg-hr.	Aborted 2½ months later	L.	D.
Pouey, H. 1927	6½	10/3/23—Radium. In 3 days total 28.4 mc-destroyed. One day rest then in 4 days 14.4 mc-destroyed. Total—43.2 mc-destroyed. 1/10/24—26.4 mc-destroyed rectal necrosis from radium (ap and pp)	Delivered Nov. 28, 1923; 18 days before term, in labor for 20 hr.	L.	L.
Bailey, and Bagg 1923	6½	Radium emanation—"Bare tubes," and platinum tube radium 2356 mc-hr. Next day, 960 mc-hr. bomb applicator to cervix; 297 mc-hr. "Bare tubes" to cervix (ap)	Eclampsia—cesarean section—6 weeks after radium	D.	D.
Favreau, M. Lamelin, P. 1932	4	2/10/26—4800 mg-hr. radium. 1/27—radium, 20 mg. times 15 days. 0.5 mm. lead, vaginally at 1.5 cm. from vault (ap)	6/10/26—delivered of living child. 10/26 hysterectomy	D.	L.
Metzger 1923	3	Radium 18 mc-destroyed. Cancer disappeared after 5 weeks (ap)	Delivered at term by incision in rigid cervix and by forceps	D.	?
Peralta 1927	7	July 24. Ra bromide—100 mg. for 24 hr. Aug. 8—100 mg. for 24 hr. 1 mo. postoperative—deep therapy x-ray repeated 2 days later 3 hours (ap and pp)	Aug. 19—fetus died in utero. Aug. severe uterine contractions, Wertheim without cesarean section	L.	D.
Peralta 1927	9	6 weeks postoperative deep therapy x-ray repeated 1 mo. later	At term Wertheim and cesarean section	L.	L.
Heraud, C. 1933	6	11/25/32—radium 25 mc-destroyed (ap)	Delivered at term, preliminary ligation of hypogastric arteries, then Wertheim	L.	L.
Lukas, Josef 1924	6	At 6½ mo. radium—20 mg.+10+10+10 ×70 hr.: total 3500 mg-hr. 3 mo. later, 4×6 mm. ulcer, leukoplakia of post. lip then given—10 mg. intrauterine, 20 mg. in cervix, 10 mg. across cervix, 10 mg. in each vault total, 3500 mg-hr. (ap and pp)	(Dilation and curettage in May, 1932.) Delivered of premature child at 7½ mo.	L.	L.
Peter, R. 1935	9	Postoperative x-ray therapy	Vaginal hysterectomy and delivery. Wertheim	L.	L.
Peter, R. 1935	8	Radium and x-ray administered in 7th mo. Repeated postoperative (ap and pp)	Membranes ruptured 15th day after treatment. Cesarean	D.	L.
Lacomme, M. Pallud, O. 1936	?	Radium—aborted 2 mo. later	Delivered at term of second child (pregnant again 1 year later)	L.	O.
Wollebeck 1935	9	Postoperative x-ray	Cesarean section, complete hysterectomy	L.	L.

Table IV—(*Continued*)

Name	Mo.	Radiation Therapy (ap = ante partum; pp = post partum)	Operative Procedure	Result on	
				Mother	Child
Pomeroy, L. A. 1936	4½	Postoperative: x-ray 32 treatments, 4 fields each received 2400 r. total—9600 r. Radium—1 long tube 83 mc. screened, 1.5 aluminum 5 mm. silver, 1 mm. brass applied so as to occupy entire length of uterine canal—34 hours—2490 mc-hr. Cervical implantations 8 mc. gold—2112 mc. total radium—4602 mc-hr.	Abdominal hysterotomy	L.	D.
Rheuter 1922	9	Postoperative—radium therapy—8/22/22 and 9/26/22. No dosage given	Cervical embryotomy	D.	D.
Heuze 1929	?	Postoperative—1 year, radium therapy. No dosage given	Cesarean section at term	D.	L.
Heuze 1929	9	Postoperative—radium no dosage given	Cesarean section at term	D.	L.
Heuze 1929	3	Radium at 3rd month, no dosage given (ap)	Cesarean section at term	L.	L.
Bottaro and Bengoa 1919	6	Preoperative radium. Postoperative x-ray. 9/1/17—50 mg. 24 hr. 48.5 mc-destroyed. 9/9/17 and 9/22 and 10/5 and 10/16 with total 24 mc-destroyed	Cesarean section at term	L.	L.
Addessi, G. 1930	8	Postoperative x-ray; no dosage given	Total hysterectomy and adnexotomy	L.	L.
Roche 1921	5	Radium—110 mc. in cervical growth for 44 hr. 19.35 mc-destroyed (ap)	Delivered at term	?	L.
De Rouville	5	100 mg. in vagina 9.6 mc-destroyed (ap)	Miscarriage	L.	D.
Biro, S. 1918	9	5 months postoperative 183 mg. 24 hr.	Cesarean and Wertheim	D.	?
Biro 1922	9	17 days post partum 84 mg. 20 hr. in vagina. 1 mo. later, 70 mg. 24 hr. ×2	Cesarean and Wertheim	L.	L.
Biro 1922	5	42nd day 84 mg. 24 hr. in vagina 2016 mg-hr. 6 weeks later 70 mg. 24 hr. in vagina 1680 mg-hr. 9 weeks later 84 mg. 24 hr. in vagina 2016 mg-hr. (pp)	Wertheim after preparation of vaginal cuff	L.	
Biro 1922	8	3 weeks post partum 84 mg. 24 hr. 2016 mg-hr. 1 month later 98 mg. 24 hr. 2352 mg-hr. 3 months later 70 mg. ×24 hr. 1680 mg-hr.	Cesarean and Wertheim	L.	L.
Biro 1922	3	15th day 84 mg. ×24 hr. 2016 mg-hr. 1 mo. later 70 mg. ×24 hr. 1680 mg-hr. 3 mo. later 70 mg. ×24 hr. 1680 mg-hr. (pp)	Vaginal hysterectomy	L.	
Biro 1925	4	On 19th day x-ray series (5 fields) 2 days later radium 70 mg. 24 hr. 1 month later 84 mg. 24 hr. 2 days later x-ray series (5 fields) (pp)	Wertheim	L.	

TABLE 4 (*Continued*)

Name	Mo.	Radiation Therapy (ap = ante partum; pp = post partum)	Operative Procedure	Result on	
				Mother	Child
Biro 1925	4	37th day 84 mg. 24 hr. 2 months later 98 mg. 24 hr. (pp)	Wertheim	L.	
Biro 1925	5	12th day post partum x-ray series; 6 weeks later repeated	Wertheim	D.	
Nielsen 1916	6	Ante partum radium. 4/23/1916 to July 1, 2480 mc-hr. of which 1512 mc-hr. intracervical; post partum 3768 mc-hr.	Spontaneous delivery	D.	L.
Nielsen 1929		Vaginal applications 5040 mc-hr. parametria free clinically (ap and pp)	Cesarean. Parametrium rigid at operation. Recurrence treated 11 mo. later	L.	L.
Commandeur 1925	8½	15 days postoperative 100 mg. in cervical stump, 75 mg. in vagina 72 hrs.	Cesarean and Porro section	D.	L.

irradiation or cesarean section and operation. Much will depend on the operator. The prognosis is poor—60 to 70 per cent mortality.

Third: When the growth is inoperable and the child viable then we should explain the condition to the husband to obtain permission for a cesarean section. Because of the dangers of rupture of the uterus, or a tear starting in the cervix and extending into the uterus or of hemorrhage or of sepsis, in these days of asepsis one should never wait to deliver the child per vaginam. With the uterus emptied, the mother should be treated as soon as her condition warrants by intrauterine radium and deep roentgen therapy. The maternal mortality here is about 65 per cent.

Fourth: If the growth is inoperable and the child inviable the chance of saving the mother by irradiation without emptying the uterus is nil. It must be admitted that unless one believes that pregnancy will check the growth the irradiation should be as thorough as in the nonpregnant. No one would be content with cervical irradiation alone in the latter. If radium is applied intrauterinely, abortion will probably follow. Therefore, if treated thoroughly enough the products of conception will be lost. The fetus should not be considered.

Here, then, we are impressed by the aid irradiation gives when the surgeon is prevented from operating or when surgery is contraindicated. Because of the fetus or child it cannot be used so thoroughly nor so efficiently as in the nongravid. However, it becomes a method second to surgery, and always as an adjunct to surgery in any of the four groups. Nevertheless cures have been obtained with irradiation and cesarean section and irradiation should be used, especially when the choice of the patient requires it. By this method the birthrate has been high. The dangers to the child by irradiation must be remembered.

SUMMARY

1. Carcinoma of the cervix during pregnancy is rare.

2. The effect of pregnancy on the growth of the cancer and the effect of the growth on pregnancy have been discussed.

3. The usual main symptom which brings the patient to the doctor is hemorrhage.

4. The diagnosis can be made only by visualizing the cervix.

5. Prognosis is good when the condition is operable.

6. Operability is higher in this group than in the nonpregnant.

7. The treatment depends on the operability of the growth and the stage of pregnancy.

a. If the growth is operable and the child inviable, disregard the child and remove all pelvic organs. Then administer postoperative irradiation.

b. If the growth is operable and the child viable precede the operation with an abdominal cesarean section.

c. If the growth is inoperable and the child viable perform an abdominal cesarean section and use postoperative irradiation.

d. If the growth is inoperable and the child inviable, the choice rests with the family. Preference should be given to thorough irradiation to cause abortion, and then further irradiation as indicated. If pregnancy is in later months irradiate and perform cesarean section as soon as the child is viable. Then irradiate again if necessary.

8. Delivery should not be allowed through the cervix.

9. Any restriction in the treatment of the patient in order to save the offspring will be at the expense of the mother.

10. The higher the birth rate in any given group in this series, the higher the maternal mortality usually is.

11. After the seventh month of pregnancy irradiation does not improve results either with or without surgery.

12. Before the seventh month irradiation following operation slightly improves maternal results.

13. Radical operation should not be delayed for irradiation.*

* For discussion see page 571.

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Vol. 43, No. 4

A FURTHER REPORT ON THE RADIUM TREATMENT OF CARCINOMA OF THE CERVIX UTERI

ONE HUNDRED AND THIRTY-FIVE ADDITIONAL CASES WITH FIVE YEAR FOLLOW-UP*

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IN A PREVIOUS publication,[1] we reported a five year follow-up on 173 cases of cancer of the cervix treated by means of long platinum filtered radium needles of low intensity acting over a long time interval. Today we wish to report a five year follow-up on 135 additional cases treated in 1931, 1932, and 1933 by the same method, and to bring out again the advantages of the method as well as to show that in our hands there has been no higher immediate mortality or incidence of complication than is experienced in other forms of radiation therapy for cancer of the cervix.

We wish it understood that these are chronologically consecutive cases as they come into the clinic. The total 173 for the first report, and the 135 for this report, represent all cases seen at the clinic, whether treated or untreated subsequently by us, or whether sent to our clinic after unsuccessful treatment elsewhere. The totals also include all cervical stump cases.

The 173, and the 135 then, are the absolute figures required in reporting such series. If the number of cases untreated because too advanced or for other causes is deducted from the absolute figure, the *relative* figure or the number of cases actually treated is obtained. This is 173 minus 8, or 165 for the first series; and 135 minus 11, or 124 for the present series. The absolute figure for the two groups is 308. The relative figure is 289, i.e. 308 minus 19.

If the cases of cancer of the cervical stump are not included, it being felt by some writers that they present a special problem and consequently should be set aside in a group by themselves, then the relative figure becomes 289 minus 11, or 278, there being 11 cases of cancer of the cervical stump included in this series.

Finally, if it is desired to show the relative results on cases treated primarily by this method and for which we have been responsible throughout, it is necessary to deduct the number of cases which have come to us after being treated elsewhere There have been 14 such cases.

THE METHOD

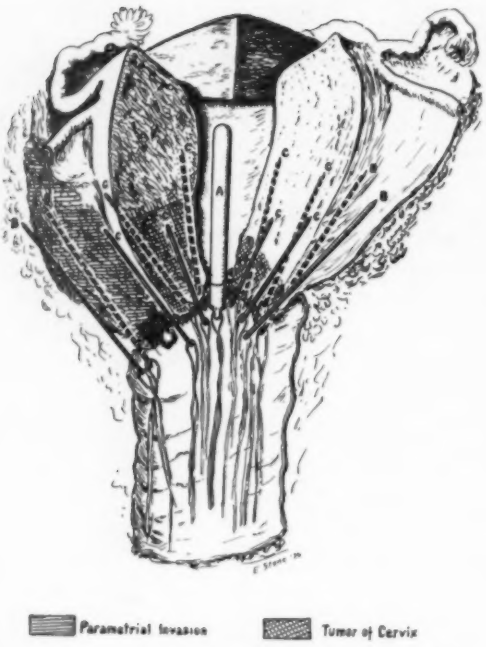
There has been no change in the method as reported and described two years ago except that roentgen therapy has been used somewhat more freely. It is not felt that the roentgen therapy has materially affected the five year results as the dosages employed in those years would hardly be considered adequate today. By the use of the interstitial radium needles implanted into the paracervical and parametrial tissues together with the use of a capsule in the cervical canal, a dosage of 3,300 mg-hr. in the cervical canal, and of about 6,000 mg-hr. in the parametrium is obtained. The distribution of the needles is illustrated in the accompanying figures. But one application is planned and this lasts six or seven days, the radium, of course, being undisturbed during this time.

RESULTS

The results of treatment of 135 additional cases are shown in the accompanying charts. A comparison of results obtained in the different clinical stages shows very

[1] Pitts, H. C., and Waterman, G. W. Treatment of cancer of the cervix uteri at the Rhode Island Hospital. *Surg., Gynec. & Obst.*, 1937, *64*, 30–38.

* Read at the Twenty-fourth Annual Meeting, American Radium Society, St. Louis, Mo., May 15–16, 1939.



Figs. 1–3. *A*, 20 mg. platinum filtered tube; *B*, 3 mg. platinum needles; *C*, 2 mg. platinum needles. (Courtesy of *Surgery, Gynecology and Obstetrics*.)

Fig. 1. Lined area indicates advancing parametrial invasion; cross-hatched area, cervical tumor; dotted needles are posterior to midline of cervix.

little difference from the results obtained in the previously reported 173 cases treated by the interstitial method in spite of the fact that more roentgen therapy was used in these last 135 cases. Of particular

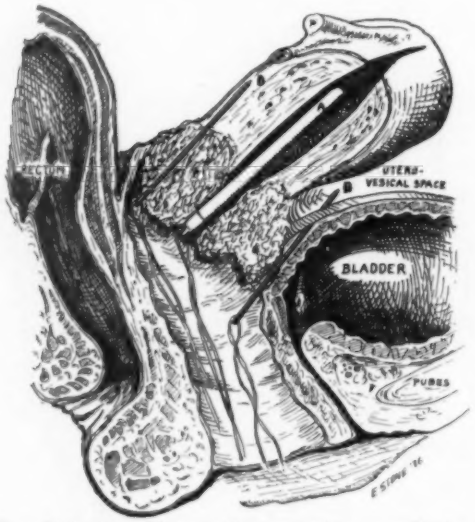


Fig. 2. Method of inserting needles anteriorly and posteriorly.

interest are the survival rates in Stage III (Schmitz) cases, that for 1926–1930 being 18 out of 62, or 29 per cent; that for 1931–1933 being 16 out of 48 cases, or 33.3 per cent. A comparison with a series of Stage III cases which we treated between 1921–1925 by a method of intracavitary application of radium, where only 6 cases out of 43 survived five years (14 per cent) shows that the survival rate for this stage has been raised over 100 per cent. The authors feel that, while it may be difficult or impossible to compare results from different clinics by clinical stages, it is possible to compare results in one clinic where the classifying into stages is done by two men working together with a common idea. We feel that our classification of Stage III cases has been consistent and reasonably dependable throughout these series. In the first

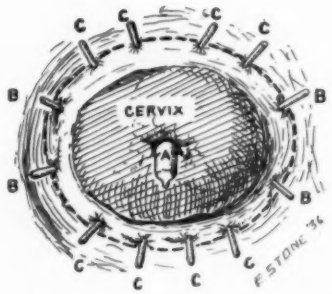


Fig. 3. Lined area shows cervical tumor; dotted line shows area of paracervical invasion.

series (1921–1925) the percentage of Stage III cases to the total was 43:120, or 35 per cent; in the second series (1926–1930) the percentage of Stage III cases was 62:173, or 35.8 per cent; and in the third series the percentage of Stage III cases was 45:135, or 33.3 per cent.

The ability to deliver approximately 6,000 mg-hr. of gamma radiation into the parametrial and paracervical tissues, in addition to the usual 3,000 mg-hr. in the cervical canal without tissue breakdown or other serious complications, is believed to be the telling factor in producing the good results by this method in the Stage III cases.

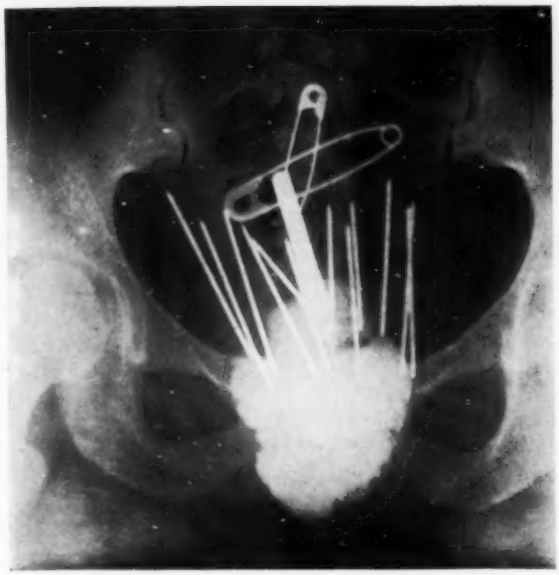


FIG. 4. Roentgenogram showing needles and capsule in place. Dense area shows iodoform packing in vagina. (Courtesy of *Surgery, Gynecology and Obstetrics*.)

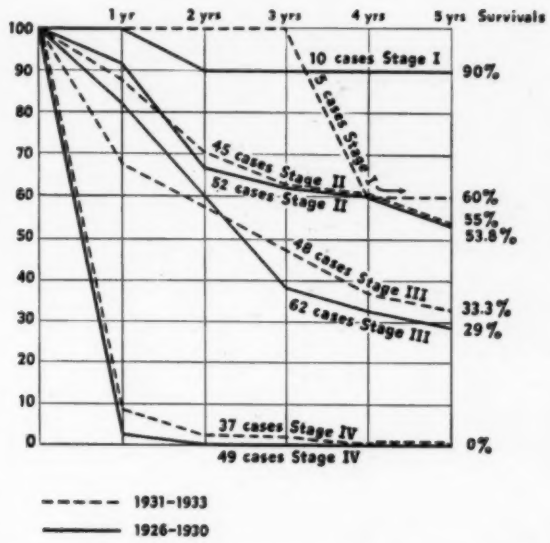


CHART I. Showing comparison between two series treated by the interstitial method. Note that the curves for Stage II and for Stage III run about parallel with slight advantage for the 1931–1933 series.

COMPLICATIONS

The insertion of long needles through the vaginal fornices into the parametria in cases of advanced and broken down cervical cancer would seem to invite disaster from infection—parametritis—peritonitis, etc. The danger of fistula formation has likewise been advanced as an objection to the method. We have now actually treated to December 31, 1938, 480 cases in our clinic. Complications of (1) immediate mortality and (2) fistula formation are as follows.

In 505 cases seen in the clinic, 25 were too advanced to treat; 480 cases were actually treated. Of these 13 cases died before leaving the hospital, a gross mortality of 2.7 per cent. Two of these patients died of massive hemorrhage, one five days after removal of the needles, one eighteen days after. As both of the patients had bled

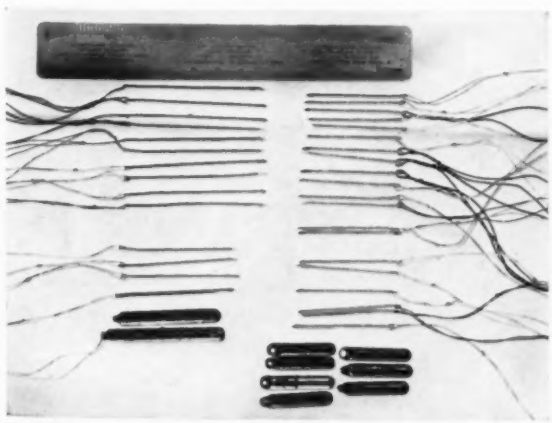


FIG. 5. Radium available. (Courtesy of *Surgery, Gynecology and Obstetrics*.)

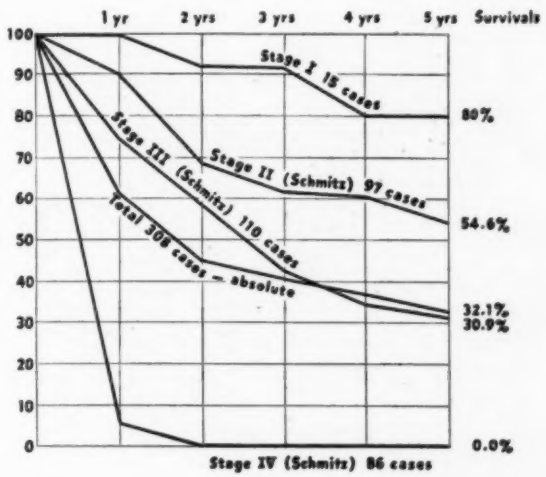


CHART II. Showing combined results of two series: 1926–1930 and 1931–1933.

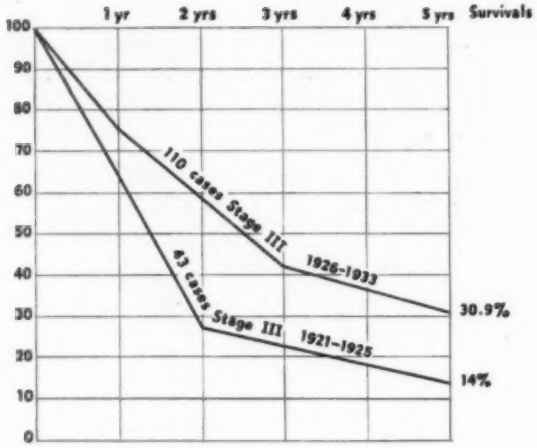


Chart III. Comparison in the results between Stage III cases treated by the interstitial method (110 cases 1926–1933) and Stage III cases (43 cases) treated by other methods (1921–1925), showing an improvement of more than 100 per cent or twice as many survivors by the interstitial method.

quite freely on admission it was not felt that the treatment had much to do with the hemorrhage. Two patients died of pulmonary embolism, one of coronary thrombosis, one of pyelonephritis sixteen days after treatment proved by autopsy with no local infection in pelvis and no peritonitis. One patient died fifty-three days after treatment of bilateral hydronephrosis and uremia and one died thirty minutes after treatment, an anesthetic death. This patient had advanced cancer and in addition had a bad heart and was diabetic. Five patients died of infection—of these one had a thrombophlebitis and septicemia and died thirty-two days after treatment, 2 had peritonitis and 2 sepsis seven and twenty days after treatment. These last 5 cases were all Stage IV cases, probably would have been better not treated, and probably would have succumbed to any method of interference. However, 5 patients out of 480 who died of sepsis gives a corrected mortality of slightly over 1 per cent which might be charged against the method.

INCIDENCE OF FISTULA

We give these figures not because we feel that they are any gauge of the destructiveness of radium treatment, because there is a definite incidence of fistulae in cervical cancer treated or untreated, but because fistula formation is an objective phenomenon, which when it develops after treatment, quite naturally in the mind of the uninitiated must have arisen from the treatment. We all know how close the cervix lies to bladder and rectum, how advanced cervical cancer often actually invades bladder and rectal walls. In the natural course of the disease many breakdowns of bladder and rectal wall occur. Of course an effective dose of radium applied against or into a cancer invading bladder wall may easily break down the cancer tissue and leave a fistula. We have always felt, however, that interstitial needles of low intensity placed in the vesicovaginal or rectovaginal septum were far less likely to cause breakdown and fistula formation than were larger plaques, bombs, or applicators of greater intensity. We offer then this actual experience for what it may be

Table I

Results: 5 Year Survivals Interstitial Method

1931–33	135 cases—absolute	44 survivals	32.6%
	124 cases—relative	44 survivals	35.4%
Stage I	5 cases	3 survivals	60.0%
Stage II	45 cases	25 survivals	55.0%
Stage III	48 cases	16 survivals	33.3%
Stage IV	37 cases	0 survivals	0.0%
1926–30	173 cases—absolute	55 survivals	31.8%
	165 cases—relative	55 survivals	35.7%
Stage I	10 cases	9 survivals	90.0%
Stage II	52 cases	28 survivals	53.8%
Stage III	62 cases	18 survivals	29.8%
Stage IV	49 cases	0 survivals	0.0%
1926–33	308 cases—absolute	99 survivals	32.1%
	289 cases—relative	99 survivals	34.2%
Stage I	15 cases	12 survivals	80.0%
Stage II	97 cases	53 survivals	54.6%
Stage III	110 cases	34 survivals	30.9%
Stage IV	86 cases	0 survivals	0.0%

Results: 5 Year Survivals Other Methods

1921–25	120 cases—absolute	24 survivals	20.0%
Stage I	4 cases	4 survivals	100.0%
Stage II	19 cases	12 survivals	63.1%
Stage III	43 cases	6 survivals	14.0%
Stage IV	54 cases	2 survivals	3.7%

worth. We feel that these figures are quite accurate. We have an excellent follow-up service and get word of what happens to our patients in about 98 per cent of all cases.

In a total series of 480 cases treated (1926–1938 inclusive) 38, or 7.9 per cent, developed fistula: 13 cases had vesicovaginal fistulas alone, 13 cases had rectovaginal fistulas alone, 11 cases had both vesicovaginal and rectovaginal fistulas and 1 case had an ileovaginal fistula. Six of the 38 cases were untreated or developed fistula following hysterectomy performed because they were not doing well and surgery seemed to offer some hope. Six cases closed spontaneously or were closed by operation.

CONCLUSIONS

We do not feel that interstitial irradiation as employed in this series is excessively dangerous or productive of high immediate mortality from sepsis or that the incidence of fistula formation is more than naturally occurs or would occur with any method of radium treatment.

We have given five year results on a new group of 135 cases seen and examined at our clinic at the Rhode Island Hospital. The good five year survival rate of a previously reported series of 173 cases is here repeated. Charts are shown illustrating the curve of survival rates for each group and stage for each of the five years.

Special attention is called to the increased survival rate in Stage III cases over that for the same stage treated by other methods in our own clinic.

We have used the absolute figure of 308 in calculating survival percentages in these charts. If 19 cases too advanced to treat, 11 cervical stump cases, and 14 cases treated elsewhere with radium and/or roentgen irradiation before coming to us, are deducted from the 308, we get a relative figure of 264 which represents cases of carcinoma of the cervix actually treated primarily by our method. If we deduct from our total survival figure of 99, the 2 survivals in the group of cases of the cervical stump and the 2 survivals in the group of those treated elsewhere, we obtain a figure of 95 survivals of cases treated primarily by our method.

The relative survival rate is, with these deductions, 95:264, or 36 per cent.

DISCUSSION ON PAPERS OF DRS. TAUSSIG, FRICKE AND BOWING, STRAUSS, AND PITTS AND WATERMAN

Dr. A. N. Arneson, St. Louis, Mo. The symposium presented this morning has brought to our attention some of the most important problems in cervical cancer. Carcinoma of the cervix complicated by pregnancy is a relatively rare condition. Few individuals have had the opportunity to see more than one or two such patients. The diagnosis of cervical cancer with pregnancy presents an emergency, and it is essential that we become familiar with the experience of others. Carcinoma of the cervical stump always presents a difficult problem in treatment. Dr. Fricke has reviewed statistics published for cancer of the cervical stump, and it has been very gratifying to hear the improvement in clinical results reported for different methods of treatment.

Two of the papers presented this morning have described methods that represent something of a departure from more conventional methods of treatment for primary carcinoma of the cervix. Each method is used in the attempt to increase the percentage of cures by control of the tumor within a greater volume of tissue. Dr. Taussig's method, for example, presents a technique for surgical removal of lymph node metastases beyond the effect of radium applied within the uterus and in the vagina. Dr. Waterman and Dr. Pitts have attempted to deliver greater doses of radiation to those regions by inserting radium needles into the paracervical and parametrial tissues.

For some time there has been fear of severe reactions following the use of interstitial irradiation in cervical cancer, and fear of introducing infection by the insertion of needles. Dr. Waterman has presented additional data to show that they have not had a high incidence of sequelae following their technique of treatment, and they have certainly obtained clinical results that are among the best reported here or abroad.

Following an earlier publication by Dr. Pitts and Dr. Waterman we began about three years ago to use radium needles in some patients. The method has not yet been applied to all cases as a routine procedure. At first we began cautiously with an empirical type of treatment. At a later date the attempt was made to work out a more elaborate scheme for delivering a predetermined dose. It is obvious that it is not always possible to calculate tissue doses very accurately, but little by little the method has been used in an increasing percentage of patients. Sufficient time has not elapsed for us to say anything about permanent cures, but it can be said that we have obtained very satisfactory results. In many instances a better result has been obtained than might have been expected from radium applied only in the uterus and in the vagina.

One might expect an improvement in clinical results from the use of needles due to the multiple sources of radium distributed widely throughout the tumor-bearing region. Due to the contribution from the different sources no single one need be used for a dose apt to produce extensive necrosis. By that means a more uniform distribution of radiation can be obtained with less discrepancy between the minimum dose reaching some parts of the tumor and the maximum amount falling on other points. If variations in the distribution of specified doses can be lessened, it is also possible to increase the minimum quantity delivered to the tumor. For the technique in question the improvement is chiefly in the parametrial regions. Any attempt to increase the percentage of cures obtained in the treatment of cervical cancer must have as its aim a method that will result in improvement in the parametrial dose.

In our experience the use of interstitial irradiation has not been followed by serious complications. Among a total of more than 50 patients bleeding has occurred upon removal of the needles in about 4 or 5 instances. The appearance of bleeding with removal would indicate that it was due to erosion into a blood vessel during the time the needle was in place rather than to puncture by insertion. Fever has been of no importance except in a few patients with badly infected lesions, and in all probability needles should not have been used in those individuals. In 2 instances we have had a mortality that appeared to be due to treatment. Both patients had extensive lesions that were unquestionably over-irradiated. Uremia occurred in each instance, and the patients died within a short time after treatment.

There are two questions I should like to ask Dr. Waterman. It has been our practice to bury the needles beneath the mucous membrane. If they are not pushed in that deeply, short sources are apt to fall out of place. At the same time a needle inserted in that manner may be difficult to remove due to the fact that the head may not be in line with the suture protruding through the puncture wound. In some instances we have had to cut down on the mucous membrane with great risk of severing the suture. I should like to ask Dr. Waterman if he, too, has had that difficulty. It may be that we have used insufficient vaginal packing, and with a firmer gauze support it may not be necessary to bury the needle completely.

The second question I would like to ask is whether or not he has ever lost a needle and if he has, what success he had in recovering it. That such an accident might occur has been our greatest fear.

DR. W. H. WEHR, Buffalo, N. Y. I would like to comment briefly on our experience with carcinoma of the cervix associated with pregnancy,—very limited, of course, but in the period of 1930 to 1933 there were admitted to the clinic almost 700 patients suffering from carcinoma of the cervix and only 2 of these were pregnant at the time of admission. Both patients were three months pregnant; the first one showed a lesion of the posterior fornix and adjacent vaginal wall, and while a rather small lesion, the anatomic extent of it would definitely put it into a Schmitz Stage II.

This lesion was implanted with gold seeds for a total of 1,320 millicurie-hours and we hoped that this would hold the growth in check until the patient was delivered and following delivery that this patient would be thoroughly treated with interstitial, intercavitary and external irradiation by means of high voltage roentgen rays.

Within six or eight weeks following the implantation of seeds, the lesion completely disappeared.

The patient was delivered in the normal manner and is now six years and seven months past the date of her treatment and there has been no recurrence and, needless to say, there has been no further treatment given.

The second patient also had a Stage II lesion, much more extensive, involving the entire cervix with infiltration of all fornices but no definite infiltration of either parametria.

This lesion was implanted with a total of 2,320 mc-hr. and the bleeding and discharge ceased. At the time of the delivery, this patient had a cesarean section. The surgeon reported to us at that time that there was no evidence of recurrence. However, within a month there was a definite recurrence and this patient was treated in the usual manner at our clinic,—with interstitial radon, intercavitary radium and high voltage roentgen rays.

There was some palliation but the patient succumbed in one year and three months.

In addition to these 2 patients there were 16 others who had carcinoma of the cervix and pregnancy but had not reported to the clinic until after delivery or until after miscarriage. Six of the patients were admitted following miscarriage, all of whom gave a history of bloody and watery discharge during their period of pregnancy. In these 6, the time interval between miscarriage and the time of admission extended from two weeks to one year; with the exception of the one patient who presented herself within two weeks, all were far advanced cases.

This one exception belonged in Stage I and this patient is now alive for eight years. There were 3 Stage III and 2 Stage IV cases, all treated in the usual manner and they all have died in a period of four days up to five years and three months.

One patient had palliation for a period of three or four years; subsequently developed recurrence and succumbed in five years and three months.

There were 5 patients who were admitted following normal deliveries and 2 patients who had had cesarean section previous to admission, one at one month and one at five months previously. In the 5 patients who had normal deliveries, from the time of delivery to admission the time extended from one and a half months up to eleven months. All of these patients gave a history of bleeding and discharge throughout the entire course of their pregnancy.

There were 5 State III and 2 Stage IV cases, and of these one Stage III case is alive and well for nine years; the rest of the patients died in periods of four months to one and a half years.

Now in addition to these there are 2 patients who had had a delivery one year previous to admission and hysterectomy six months previous to admission. In other words, six months after the delivery; and a third patient who had a little bloody discharge two weeks before the expected date of delivery and in whom an early carcinoma was discovered. This patient had a cesarean section and total hysterectomy and following this a prophylactic course of high voltage roentgen rays and she is well for a period of eight years.

There were 2 other patients who, following miscarriage, were curetted and tissue taken from the cervix, and in both instances there was a questionable diagnosis of epithelioma of the cervix and both of these patients refused treatment on the basis that the diagnosis was questionable and they wanted children. They have been followed for two and three years, respectively, and there is no evidence of tumor.

A group such as this is too small to permit definite conclusions to be drawn, but of the patients with miscarriage there was one with a Stage I early lesion; that patient is well for eight years. Of the Stage II cases (those are the 2 patients who came to us pregnant with an associated carcinoma of the cervix), one patient is alive for six years and seven months.

Of the Stage III cases there were 8. One patient is alive for nine years, which would, on that small series, give about 12.5 per cent; and of the 4 Stage IV cases, there are none alive.

Of the 3 who had hysterectomy, there was only one early case and that patient is alive for eight years.

It has been our experience that the most important single factor in prognosis in carcinoma of the cervix, and it seems to apply here in carcinoma of the cervix associated with pregnancy, is the degree of anatomic involvement.

Dr. Herman C. Pitts, Providence, R. I. I want first to express our appreciation of this opportunity to give our results in the interstitial use of radium in cancer of the cervix.

In discussion I had in mind to say something of the difficulty in removing the long needles from the tissues after irradiation, and so I should like to answer Dr. Arneson's question of Dr. Waterman. We have found trouble at times in removing these needles,—in fact, so much trouble that we have had to resort to opening the abdomen in several cases to get the needles out finally, after hunting for them

through the pericervical tissue from below.

We have found now that by the use of Deknatel for threading the needles, that difficulty has been obviated. Deknatel has a tremendous tensile strength and by threading with this we haven't had any difficulty in several years. We tried at one time to use fine metal wire and that was the worst of all. That broke without any rhyme or reason.

When the end of the needle catches in the mucous membrane, if it has been pushed through under the mucous membrane, we have found that by coaxing with the finger, pushing it back and pulling it down, gently, we have been able to get it through the hole of entrance without making any incision in the mucous membrane, but that has been a difficulty that is quite apparent.

In respect to complications, there is one other I should like to speak of that Dr. Waterman touched on. That is the possibility of injury to the ureter. In one of my private cases the application of radium was followed by a stricture of the ureter that was perfectly apparent and which I relieved by opening the abdomen and transplanting the ureter into another place in the bladder wall. That worked perfectly well. She had no further difficulty.

I might say further that that patient finally died, in another city, of symptoms that suggested that she had had some injury to the intestinal wall followed by an obstruction and probable perforation of the intestine. The doctor who took care of her at that time wrote me the symptoms and I judged that something of that kind happened, although no operation was done. She had survived four years, when she died of this complication.

Before I came here I reviewed my own private cases from 1926 to 1934. There were 72 cases treated with radium needles, and this review upset a number of preconceived notions that I had regarding private cases. In the first place, I supposed that among the private cases I would find a larger percentage of Stage I cases. To my surprise, among the 72 cases I had just one Stage I case. There were 27 Stage II, 29 Stage III and 15 Stage IV cases.

The operability was quite high—38.8 per cent. It should have given me a better five year survival rate than 29.1 per cent.

I can only say that the one Stage I case I had survived the five years, which gave me 100 per cent on that. There were no survivals in the Stage IV group. In that series there was no immediate mortality and aside from that one complication in the ureter there were no other complications that I noted.

There was one other thing of interest that I would like to speak of again that Dr. Waterman touched on. That is the surprising lack of complications from the entrance of these needles into the peritoneal cavity. We had occasion at one time to try a short series by implanting our needles and then opening the abdomen and tying off the circulation to the uterus. We tied off the ovarians and uterines on both sides, feeling that by that measure we might get a greater effect from our irradiation.

We did that on a short series and were rather appalled to find that in every case there would be a certain number of these needles sticking up into the peritoneal cavity but apparently they did no harm because there have been no untoward results reported in this series of ours.

Dr. William P. Healy, New York City. I am very much interested in Dr. Taussig's paper. I think it is very nice indeed that his paper was presented here because he is making a splendid effort to improve his percentage of cures in the Stage II cases, and Dr. Pitts and Dr. Waterman were concerned about their Stage III cases, so we have had presented to us this morning two different approaches to the problem of the cure of carcinoma in the cervix but both in a sense touching upon, you might say, a surgical approach.

Dr. Taussig and all of us know that 30 to 50 per cent of cases of cancer of the cervix always have metastatic pelvic glands, and we all have realized that we are not getting in through the external portals enough radiation to clear up metastatic cancer in pelvic glands.

Therefore, I think that the approach that he is making is entirely justified, and I am delighted that it is being done by a man of Dr. Taussig's ability and repute, because if in time these results indicate that it is a procedure that should be followed, probably more of these operative procedures will be done. It isn't exactly the same thing, of course, as the dissection of the axilla in cancer of the breast, because there we take out the entire contents of the axilla, whereas Dr. Taussig restricts himself (I think) to lymphadenectomy alone.

I think it is impossible, by any paper work, to explain the difference in operability rates of

the cases in and about Providence and elsewhere.

Percentages that run from 36 per cent or almost 37 per cent to 38 per cent of operability are far above what we see around New York City and it was interesting that in that high total of all the cases presented by Dr. Waterman, not a single Stage IV case had survived; the Stage III cases are not as extensive, presumably, as the Stage III cases in the League of Nations classification, which must have a solid perimetrial fixation out to the bony pelvic wall on one side or the other in order to be Stage III.

But regardless of all our comment as to classification and grouping, we are delighted to be in a position to compliment Dr. Pitts and Dr. Waterman on their high percentage of cures which really does parallel their operability, because our own cures also largely parallel our operability.

When you get into the groups that have lymph gland involvement you are not going to cure them, in my opinion, with irradiation alone. You may add somewhat to the end-results with a lymphadenectomy or a Wertheim hysterectomy but not with irradiation.

Dr. Taussig (closing). I should like to add just a word to what Dr. Healy has just now said. That refers to the attempt to compare results from different institutions.

In the first place, the character of material coming to a cancer hospital is very different from that coming to a general hospital. We know that from experience in St. Louis. Many more advanced cases come to a cancer hospital. In the second place the method of classification of cases, of grouping, even when doctors say they are using the League of Nations classification, is not uniform in different institutions. My lymphadenectomy cases would be called Stage III according to the classification that has been usually employed by others. I call them Stage II because according to Heyman that is the proper terminology.

It seems to me the value of contributions in regard to the treatment of cancer arises from comparison of work in the same institution. If you change your treatment, under a fixed control, with the same method of grouping cases, and if you find this change of method causes improvement in your results, then you can say, if the cases are sufficient in number, that you have a definite improvement in technique; but to compare your results with other results in another institution means nothing at all.

Dr. Fricke (closing). I have nothing special to add except that these rare carcinomas of the cervical stump have interested us a great deal at the Clinic and there are always one or two patients who stand out. Two come to mind, one had been subjected to a supravaginal hysterectomy for fibroids two years previously and returned with a carcinoma, Grade 3, of the cervical stump which was classified as Stage III. This was treated and she returned for re-examination from time to time and the diseased condition had entirely cleared up.

In 1932 she came back with a totally different symptom and lesion. She then had an adenocarcinoma, Grade 2, of the rectum. This we treated with radium only. It has cleared up and she has remained well.

Another patient in another coincident group had been subjected to a chemical hysterectomy. This is the only case we included in which this type of operation had been performed. A year and a half later a carcinoma of the stump of the cervix developed. She was treated in 1930. The disease cleared up entirely and she was well, on frequent check-ups, for seven years or a little more than seven years. Then she returned with a massive recurrence or new growth. We treated her palliatively but she died a short time afterward.

Dr. Strauss (closing). I would like to add a word to what Dr. Wehr brought out concerning the postpartum cases. The cases of carcinoma of the cervix noted in the puerperium outnumber those discovered during pregnancy. They do not raise the same problems because the uterine cavity is empty and the life of the offspring does not come under consideration. Undoubtedly they should have been discovered during gestation.

There are some cases reported in which supracervical hysterectomy was done and this was followed by irradiation of the stump. I think that is not good procedure as Dr. Fricke has just brought out.

Dr. Pomeroy's case, which is in my paper, is very interesting from another viewpoint because it has not been reported before. It was treated in 1936 with an idea of quickly procuring a condition that would permit thorough irradiation. The patient was only four and a

half months pregnant and an abdominal hysterectomy was done and the fetus removed. I think that is better than doing a supracervical hysterectomy. Then she had thorough, heavy roentgen irradiation followed by heavy radium therapy, intrauterine, a little less than 2,500 mg-hr., and cervical treatment with radon seeds so that the treatment totaled almost 5,000 mg-hr. She is well to date.

Dr. Waterman (closing). I have been much interested in what Dr. Strauss has said about the treatment of cancer of the cervix complicated by pregnancy. We have in the last three or four years adopted a procedure somewhat similar to his. Where pregnancy has advanced four or five months and it does not seem advisable to wait for viability, we have been doing a hysterotomy high across the uterine fundus in order to keep the incision as far away from the cervix as possible. After removing the ovum the wound is closed and a ten day interval allowed for involution and healing to occur. It is then our practice to start treatment with deep roentgen therapy and radium according to our standard technique. This approach to the problem seems to us logical and we are going to see what can be done with it.

What Dr. Taussig says about classification of cancer of the cervix by different clinics is undoubtedly true. It is difficult to have agreement as to the different groups or stages even if a definite classification can be accepted by all. A classification, however, is useful in a given clinic where the work is done by one or two men who check each other and have learned to agree quite consistently. Here comparison of results in different methods or from year to year may be fairly accurate. We have adopted the Schmitz classification and have used it through the years. If our results in a given class with a certain method show improvement over the results in the same class with a different method, we feel that something has been accomplished.

Dr. Healy has spoken of the high percentage of early cases, i.e. Stage I and Stage II in our series. It is true that we have a rather large number of favorable cases. It is also true that we do not have an excessive number of very advanced cases, i.e. Stage IV. I think this shows certainly that we are not increasing or improving the Stage III good results by placing some of the favorable borderline Stage II cases in this group; nor have we improved the results in the Stage III by placing some of the unfavorable borderline Stage III cases in the more advanced Stage IV group. It will be noted that our greatest improvement has been in the Stage III cases. This is the significant point that we wish to bring out as showing the value of interstitial irradiation of the parametrium with long platinum needles.

Vol. 43, No. 4

TREATMENT OF POLYCYTHEMIA VERA BY ROENTGEN IRRADIATION OF THE ENTIRE BODY*

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SINCE the earliest description of polycythemia vera as a definite clinical entity, many different agents have been used in an effort to cure or control the disease. The most common are erythroblastic drugs, venesection, irradiation with radium or roentgen rays, oral administration of preparations of spleen, and gastric lavage. In this discussion we are principally concerned with the use of roentgen rays.

Undoubtedly because of the almost universal enlargement of the spleen in these cases, irradiation was first directed to this organ only, a practice which still persists in some localities. In 1916 Lüdin[2,6] first successfully irradiated the skeleton in addition to the spleen. His method consisted of using numerous portals, one or more at each sitting, and this plan with various minor modifications is probably the most widely used approach today. Langer,[5] in his irradiation directed toward the sympathetic nervous system, probably brought about the beneficial effects gained by the action of the roentgen rays on the vertebrae.

In 1927 Teschendorf[9] reported the use of teleroentgen therapy. As a therapeutic agent in the diseases for which it was introduced, namely, leukemia, lymphosarcoma, and Hodgkin's disease, it probably is no better than regional irradiation, and some observers consider it contraindicated.[2] Sgalitzer[2,8] began about this same time to treat polycythemia by Teschendorf's method, and he obtained good results even in cases that had been refractory to regional irradiation. By 1936 Sgalitzer had treated 44 patients, with good results in 42.

One patient died before proper conclusions could be drawn, and one refused to complete the course of treatment. Sgalitzer felt, therefore, that he had benefited all the patients who had received adequate treatment. In one instance a patient remained well for three and a half years, then had a recurrence, was treated again, and was well two years after the second course of treatment. Sgalitzer fails, however, to give protocols or records of examinations of the patients' blood.

Teleroentgen therapy was first extensively applied in this country by Heublein,[3] and like Teschendorf his cases consisted mainly of leukemia and Hodgkin's disease. Hunter,[4] in 1935, published complete accounts of two patients with polycythemia vera who were treated by roentgen irradiation of the entire body. At that time the disease in both patients had been in remission for almost three years. One patient received only the initial series of treatment; the other received a second series at the end of one year, although the patient at the time was free from symptoms, and the blood picture was normal. At least one of Hunter's cases was reported in 1933 by Sanderson.[7]

Since 1936 we have treated 5 patients with polycythemia by the method of roentgen irradiation of the entire body. We have been unable to follow the course of one patient, but we are reporting the other four in detail.

Our method of treatment conforms, in general, to that outlined by Sgalitzer, Sanderson, and Hunter. The patient is placed 2 to 2.5 meters from the anode of the therapy tube, either in a chair or on a stretcher.

* From the Department of Roentgenology, The Johns Hopkins Hospital, Baltimore, Md.

The patient faces the tube, with no lead protection of any kind. Thirty to 50 roentgens are given at a treatment, and treatments are administered every day or every second day. This dosage is measured at the patient's distance and also calculated from the intensity at 50 cm. by the inverse square law. In one instance 1 mm. aluminum only was used for filtration, but in all other instances 1 mm. aluminum and 0.5 mm. copper were used. The amount of filtration seemed to make no difference in the results. With 1 mm. aluminum and 0.5 mm. copper, 52 r were delivered in twenty minutes at a distance of 215 cm. (200 kv. (peak), valve tube, half-wave rectification, Villard condenser circuit, half-value layer of 0.5 mm. copper: 1).

REPORT OF CASES

Case 1 (JHH 65656). K. W., a white woman, aged thirty-four, was admitted to hospital for the first time in October, 1935, complaining of headache, dizzy spells, and redness and numbness of her extremities. The family and past histories were noncontributory. As early as 1933 her neighbors had commented on the redness of her hands and face. Her feet would become bluish when she was erect; she had occasional epistaxis; she would feel depressed and cry for no apparent reason; and the dizzy spells which occurred two or three times a week were not related to any particular activity. All her symptoms were becoming gradually worse at the time she was admitted.

Physical examination revealed weight loss, florid skin on the face and neck and to a less degree on the body, exceptionally red lips, much lymphoid tissue in the pharynx, and a "beefy" red tongue. The spleen was tender and extended 4 to 5 cm. below the costal margin. On admission the hemoglobin estimation was 144 per cent (21 gm.), the erythrocytes numbered 7,900,000, and the leukocytes 10,900 per cu. mm.

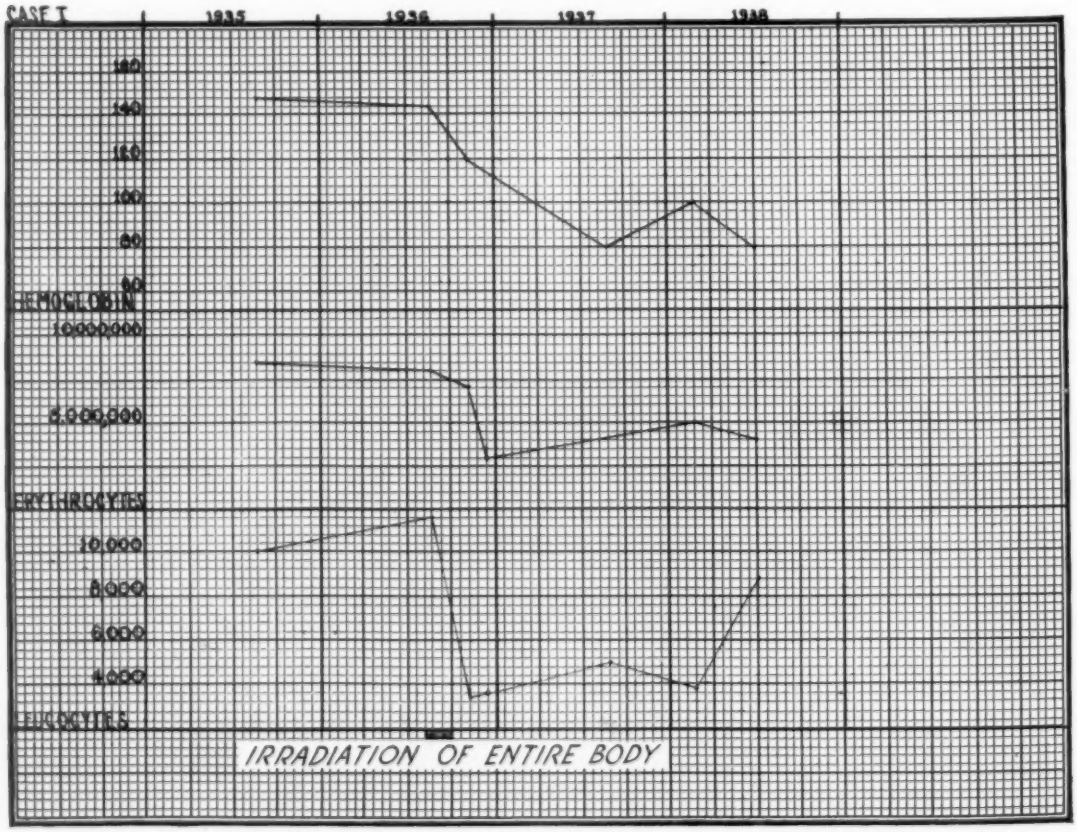


Chart I

Between October 22, and December 5, 1935, the patient received a total of 3.3 gm. phenylhydrazine, which she did not tolerate very well. Venesection was performed on December 12, and 500 cc. of blood was removed. She was discharged unimproved.

The patient returned to the hospital in July, 1936, with essentially the same symptoms and findings as the year before. During the interval there had been no relief from symptoms. The blood picture was as follows: hemoglobin estimation 130 per cent (21 gm.), erythrocyte count 7,500,000 and leukocyte count 19,000 per cu. mm.

Roentgen therapy by irradiation of the entire body was instituted on August 25, 1936, and completed on September 12, the patient receiving fourteen treatments of 52 r each. Chart 1 shows that the leukocyte count dropped steadily to 3,200 per cu. mm., but the erythrocyte count and hemoglobin remained the same. No record of her blood is available again until November, 1936, at which time the erythrocyte count had dropped to 3,400,000 per cu. mm., and the leukocyte count had risen to 4,500 per cu. mm. The patient's progress since that time may be seen in the graph, and her physician states that she has been well since November, 1936.

Case II (JHH 107653). We obtained our first record of this patient, S. S., a white woman, aged sixty-four, from a physician she consulted in 1926. Her blood picture at that time was as follows: estimation of hemoglobin 153 per cent, erythrocyte count 7,736,000, and leukocyte count 8,350 per cu. mm. During the spring, summer, and autumn of that year she received roentgen therapy over her spleen. The erythrocyte count remained essentially the same from May to December except for one recorded count of 3,000,000 in September. Shortly thereafter she consulted another physician who administered phenylhydrazine to her. Unfortunately, only a partial record of the blood picture is available until 1930.

In May, 1930, the patient entered the hospital for the first time. Her family history was noncontributory. She complained of dizzy spells and headache which she had experienced intermittently for seven years. She had been nervous for five years, and immediately previous to admission she had noticed palpitation and dyspnea on exertion. For one month before admission she had no treatment with drugs, but she had been taking ½ pound of spleen a day.

Physical examination revealed a well developed, obese woman with a remarkable brick red color of face, neck, mucous membranes, and nail beds. The tonsils were enlarged. Blood pressure was 140 systolic and 90 diastolic. Examination of the blood resulted as follows: estimation of the hemoglobin 140 per cent (19.5 gm.), erythrocyte count 7,990,000, and leukocyte count 11,000 per cu. mm.

From May 11 to 19, 1930, she received orally 640 gm. of prepared spleen. On May 17 venesection was performed; and 600 cc. of blood was removed. She was discharged unimproved. Between May, 1930, and March, 1931, she was bled twice by her family physician and received ½ pound of spleen daily for eight months.

She was readmitted to the hospital in March, 1931, with a blood picture as follows: estimation of hemoglobin 150 per cent, erythrocyte count 8,300,000, and leukocyte count 20,800 per cu. mm. Symptoms and physical findings were essentially the same as the year before except that arteriosclerosis seemed more noticeable, and the patient was more nervous and unstable emotionally. Blood pressure at that time was 175 systolic and 125 diastolic. During this visit she was given Fowler's solution, but its use was discontinued when she did not tolerate it well. Two venesections were performed, one of 700 cc. of blood and the other 1,000 cc. The patient was discharged in April without appreciable change in the blood picture.

When she was admitted to hospital in May, 1937, arteriosclerosis and mental confusion had increased. In addition, there was some pitting edema of the legs; the liver and spleen were each 4 cm. below the costal margins; the blood pressure was 260 systolic and 135 diastolic. Blood count was as follows: estimation of hemoglobin 135 per cent (19.5 gm.), erythrocyte count 8,500,000, and leukocyte count 26,500 per cu. mm.

The patient received roentgen therapy by irradiation of the entire body from May 18, 1937, through June 2, during which time ten treatments of 34 r each were given. She was discharged to the care of her local physician. Chart II shows subsequent reports on the blood picture. A report on July 7, 1938, stated that the patient, although deteriorating mentally, was maintaining a low normal erythrocyte count and hemoglobin and a normal leukocyte count.

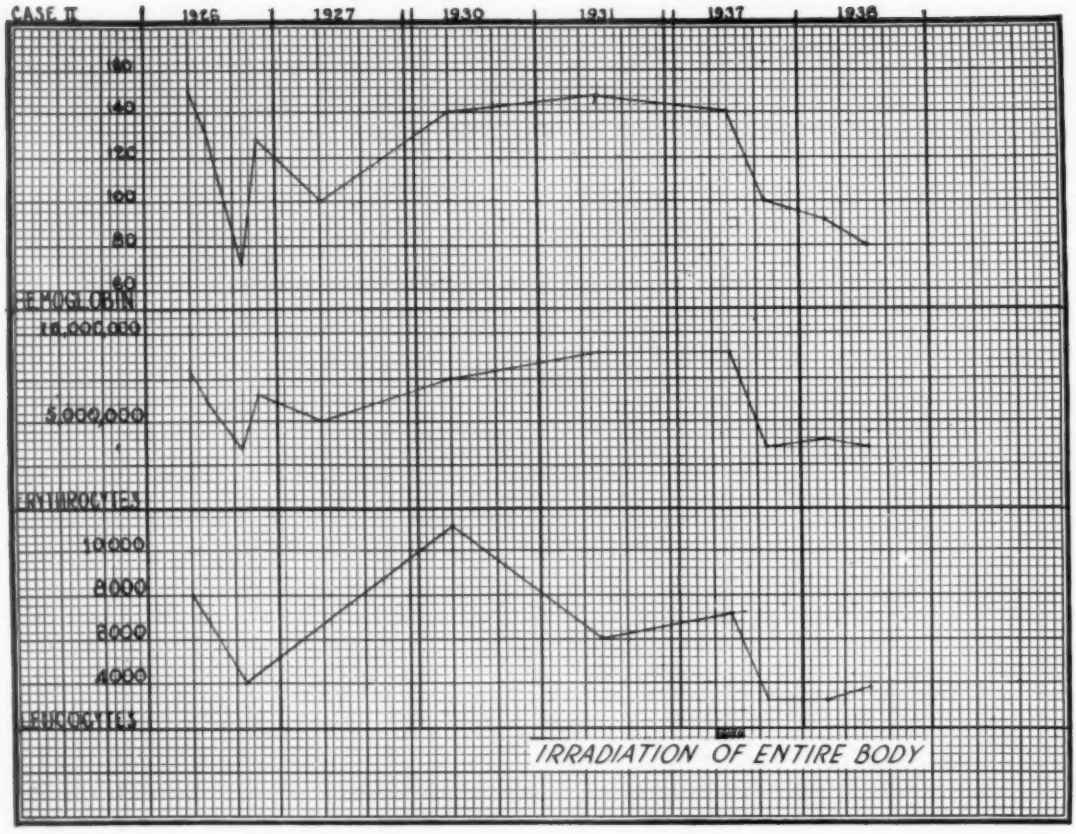


Chart II

Case III (JHH 116788). E. B., a white woman, aged fifty, was admitted to hospital in 1934 with a diagnosis of uterine myoma. The erythrocyte count was not recorded, but estimation of the hemoglobin was 82 per cent, and the leukocyte count was 9,200 per cu. mm. Hysterectomy was performed and after uneventful convalescence she was discharged without record of change in the blood picture.

From 1934 to 1937 the patient was seen in various dispensaries, but no examinations of the blood were reported. On September 1, 1937, the patient was admitted to hospital, suffering from dizzy spells, fainting spells, and "paralytic attacks." She dated her illness from the anesthetic taken in 1934. In 1935 she experienced nervous headaches, "tense" spells, choking sensations, and loss of appetite, sleep, and work. About this time she spent seven weeks in the psychiatric institute, where she complained of burning sensations as if her blood were on fire. These attacks continued until hospital admission in 1937.

Physical examination revealed a well developed woman whose face and extremities showed a distinct blush and whose tongue and mucous membranes were a deep red color. The spleen was 5 cm. and the liver 3 cm. below the costal margins. Peripheral arteriosclerosis was evident. Examination of the blood showed a hemoglobin of 138 per cent (20 gm.), an erythrocyte count of 5,460,000, a leukocyte count of 13,240 per cu. mm., and hematocrit of 58.5.

Roentgen therapy by irradiation of the entire body was instituted September 8, 1937, and continued through October 4, the patient receiving eleven treatments of 52 r each. On November 10, 1937, she reported that she felt much better. The liver and spleen had diminished in size. On December 12, two months after discharge from the hospital, the leukocyte count, which had dropped following treatment, was normal, and the hematocrit was reduced to 41.

Several furuncles developed about the face, but cleared up without difficulty. On February

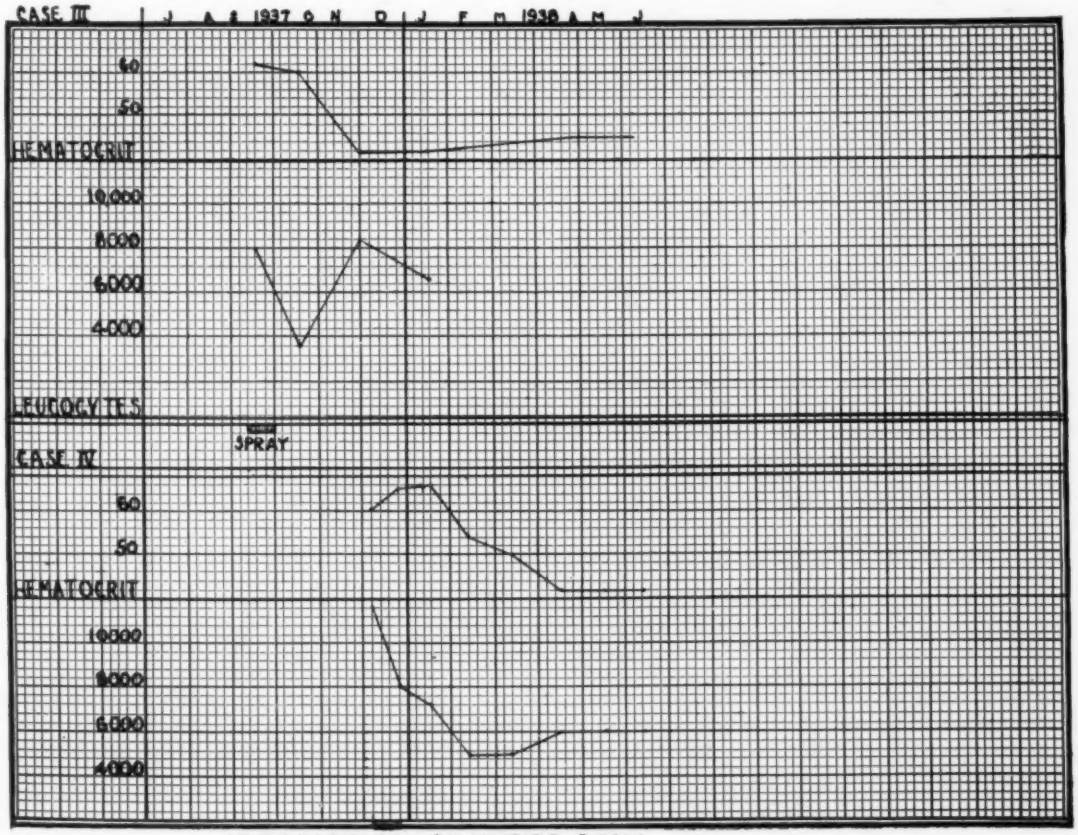
5, 1938, the liver and spleen were just barely palpable, and the blood count remained normal. During April and May the patient suffered from recurrent furunculosis. The hematocrit was 48.5 on May 6, 1938, and the leukocyte count was 8,450. On June 20, 1938, she had no complaint, and the furuncles seemed to be healing.

Case iv (JHH 127372). J. B., a white woman, aged fifty, was admitted to hospital December 8, 1937, complaining of weakness, pain in the left shoulder, headache, and some dizziness. The family history was noncontributory. In the patient's past history was a story of nervousness and emotional instability, for which she had been treated in the psychiatric institute. Beginning at the age of nineteen, she had been operated on many times, the last time in 1936. The blood count was found to be elevated at that time. For one year prior to her most recent admission to hospital she had noticed increasing weakness, fatigue, giddy spells, and immediately prior to admission bluish spots on her extremities.

Physical examination revealed a fairly obese woman with dusky red skin. The lips and mucous membranes were very red, and the sclerae were injected. The liver was 3 cm. and the spleen 2 cm. below the costal margins. Several ecchymoses were present on the left thigh. Blood count showed a hemoglobin of 140 per cent (21 gm.), an erythrocyte count of 9,120,000, and a leukocyte count of 13,450 per cu. mm.; the hematocrit was 63.

Roentgen therapy by irradiating the entire body was started December 21, 1937, and completed January 5, 1938, the patient receiving ten treatments of 52 r each. She was discharged January 11, 1938, with a leukocyte count of 8,240 per cu. mm., although other elements of the blood picture remained the same as at the time of admission.

The patient was readmitted January 16 because unfavorable conditions at home prevented proper control. She noticed that she was



IRRADIATION OF ENTIRE BODY

Chart III

losing hair over the frontal region of her head. The hair subsequently became normal, and since there was no other loss of hair, the condition was assumed to be coincidental and not due to irradiation. The ecchymoses had disappeared, and the platelet count, which was low when therapy was completed, had returned to normal. The blood changes came about slowly, but eventually showed definite improvement (Chart III). The patient was seen last on June 23, 1938, at which time she was clinically in good condition, and the blood findings were normal.

Several points which call for discussion have arisen during the treatment and subsequent course of our patients. The leukocyte level was found to be the most accurate measure for determining the amount of treatment to give in any one case. Daily leukocyte counts should be made and when the number per cubic millimeter drops below 4,000, treatment should be stopped. If this rule is followed, an overdose can be avoided. The leukocyte count continues to drop for a short time after cessation of treatment, but then gradually returns to normal. Our charts prove that hemoglobin determinations and erythrocyte counts are unnecessary during therapy, because no change is evident in these elements until one to two months after the patient has been treated.

Objection has been raised about the latent period, that is the one to two months following therapy when erythrocytes, hemoglobin, and hematocrit remain high, while symptoms persist, and the use of phenylhydrazine and venesection during this period has been suggested. However, in some instances elevation of the leukocyte count follows use of phenylhydrazine.[1] Anything which acts in such manner is dangerous when we remember that our index for therapy is the level of the leukocyte count. Venesection could be resorted to perhaps without danger, but the relief produced thereby is doubtful, and at best only temporary. We feel, therefore, that a short time of continuation of the symptoms is offset by the almost positive assurance of eventual relief.

Of the many methods used in treating patients with polycythemia, none seem to have produced so consistently the rather positive and prolonged relief from symptoms as that which has been gained from adequate roentgen therapy of the entire body in our cases and in those of Sgalitzer, Hunter, and Gilbert.[2] It is true that one of our patients (Case II) is degenerating mentally, but it is also true that polycythemia was diagnosed in her case and that she was treated by other methods for eleven years before receiving roentgen therapy of the entire body. Possibly her present condition might have been averted had the polycythemia been arrested earlier. The other 3 patients, 2 of whom (Cases III and IV) possessed mild mental disturbances are certainly improved at the present time.

How long does remission last? The length of time will probably vary with the individual. In those cases reported here there has been no recurrence in twenty-three, fourteen, ten, and seven months respectively, and should signs or symptoms return to any one of them now, repetition of roentgen therapy of the entire body, from the standpoint of dosage, is not contraindicated.

This series of cases is too small for us to draw conclusions. We consider it important, however, to present our results and to corroborate the findings of the few other authors on this subject, namely, that roentgen therapy applied to the entire body at each seance is the most effective method to date for producing prolonged remission of polycythemia vera.

The authors wish to express their appreciation to Dr. Sarah M. Peyton of Crisfield, Maryland, for her very helpful coöperation in following two of the cases reported here.

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OSTEOMYELITIS OF THE OCCIPITAL BONE COMPLICATING THE ROENTGEN TREATMENT OF A NASOPHARYNGEAL LYMPHOSARCOMA

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THE occurrence of neurological or meningitic symptoms in the presence of a nasopharyngeal neoplasm is generally indicative of erosion of the base of the skull with invasion of intracranial contents by tumor or secondary infection. Such a phenomenon is particularly common in the evolution of the epitheliomas of the nasopharynx. As Furstenberg[1] has stated, these tumors have an irresistible tendency to grow upwards and invade bone, even when the primary tumor is very small. Thus, it is not infrequent for the lympho-epitheliomas to manifest themselves initially by symptoms referable to invasion of structures at the base of the brain (basilar syndrome). This syndrome has been studied particularly by the neurologists (Woltman,[2] Needles[3]). The adenocarcinomas of the nasopharynx, which are usually slow-growing tumors, will erode the base of the skull late in the course of the disease when they have attained considerable size.

In contrast to the carcinomas, it is extremely rare for the lymphosarcomas to erode the bony confines of the nasopharynx. Neurological complications of the nasopharyngeal lymphosarcomas presenting the picture of a basilar syndrome have been reported. Thus 4 such cases were present in Woltman's series and he collected at least 10 more from the literature. However, in none of these cases were postmortem examinations performed and the exact mode of invasion of the nervous system was not elucidated. It is possible that the structures at the base of the brain were involved, not by erosion of the tumor through bone but by spread of tumor along cranial nerves and extension into cranial foramina.

The invasive powers of these tumors, with respect to the surrounding bone, is in inverse relationship to their radiosensitivity. Thus, the lymphosarcomas arising from the pharyngeal tonsils are very radiosensitive and may be totally destroyed in a high percentage of cases. Jutras[4] reports that 89 per cent of the pharyngeal* lymphosarcomas treated at the Radium Institute of Paris were permanently destroyed at their site of origin. The tendency to early and widespread dissemination was responsible for the eventual low five year survival rate (25 per cent). Among New, Broders and Childrey's series of nasopharyngeal tumors, there were 15 lymphosarcomas. Four of these patients are alive after seventy-five months. In contrast to these results, the epitheliomas of the nasopharynx are very difficult to eradicate locally with radiation therapy and death is usually due to failure to control the primary site of disease.

In the case to be reported, a neurological and meningitic syndrome determined a fatal outcome during the course of treatment of a nasopharyngeal lymphosarcoma. One was forced to conclude that, despite adequate therapy, the tumor had continued to grow and had invaded the base of the skull, a difficult series of assumptions in face of the histological type of tumor under consideration. Postmortem examination revealed a totally different explanation for the chain of events leading to the patient's death.

CASE REPORT†

S. S. (No. 28747), aged sixty, admitted to Montefiore Hospital November 11, 1937, with

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* This includes tumors arising from the nasopharynx, tonsil and base of the tongue.

† Our thanks are due to Dr. A. A. Schwartz who referred this patient for radiation therapy and with whose permission it is being reported.

a three months' history of increasing tinnitus, at first left sided and subsequently bilateral. During the four weeks preceding admission, tinnitus was replaced by deafness, which was more marked on the right. In addition, patient complained of dysphagia and severe headaches of a generalized character. Moderate nasal obstruction was present.

Positive findings on physical examination were limited to the nasopharynx, which was almost completely obliterated by a firm, edematous mass, most voluminous on the right and appearing to originate from the right pharyngeal wall. The mass was visible only on posterior rhinoscopy. It did not invade the nasal fossae. There was no cervical or remote adenopathy. Chest was negative.

Radiotherapy was started on November 1, 1937. Two large lateral fields (14×13 cm.), including the primary tumor and its lymphatic drainage, were treated. In the course of six weeks, patient received 2,300 r (measured in air) to each field. Factors were 200 kv., filter 1 mm. Cu and 4 mm. Al, target-skin distance 80 cm.; daily dose, from 150–200 r. The tumor regressed satisfactorily under treatment. However, a necrotic ulceration developed in the tumor, probably starting at the site of biopsy (Fig. 1). Deafness became worse during therapy and headaches also became more marked. There was a severe epithelitis starting on the uvula on the fifth day of treatment and reaching a maximum on the seventeenth day. The soft palate, pillars and pharyngeal wall were also involved.

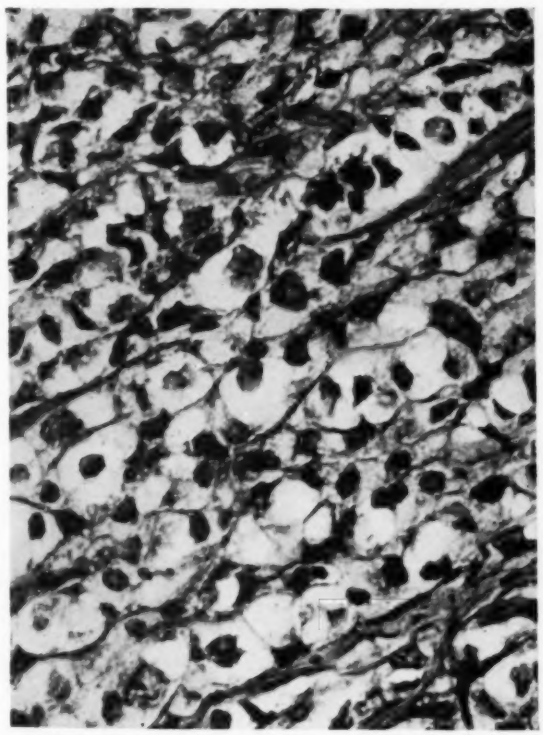

Fig. 1. Histology of tumor. Lymphosarcoma of reticulum cell type. Cells are stellate-shaped with cystoplasmic reticulum. ×480.

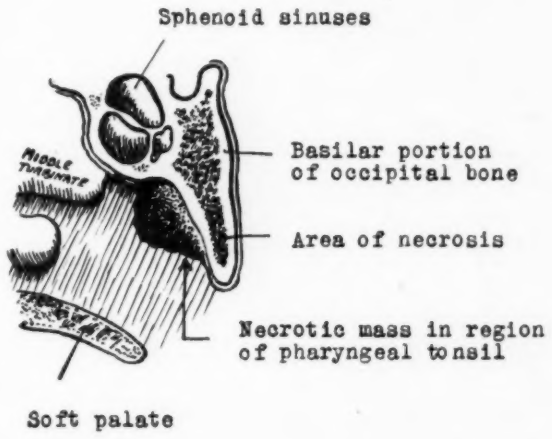

Fig. 2. Mid-sagittal section showing necrotic mass in region of pharyngeal tonsil as seen at autopsy.

Two days before the completion of treatment a paralysis of the left half of the tongue was noted. Headaches were becoming worse, especially in the right temporoparietal region. Four days later, the patient suddenly had a severe chill, became stuporous and cyanotic. The chill lasted for fifteen minutes and stupor for half an hour. Temperature rose to 105.5° F. The next day there were definite signs of a meningitis, bilateral Kernig's sign, stiff neck and Cheyne-Stokes respiration. Lumbar puncture revealed an initial pressure of 280 mm. of water, fluid was turbid, cell count 780 leukocytes with a predominance of lymphocytes. No organisms were present on smear or culture of the spinal fluid.

Signs improved in the course of the next day and spinal tap now showed normal pressure, only 260 cells, lymphocytes and no organisms. Unfortunately, the patient showed signs of a lobar pneumonia at this time and died December 13, 1937, from the pulmonary complication.

Postmortem Examination. Except for the lungs, which showed a confluent bronchopneu-

monia involving the entire left lower lobe, the positive findings were limited to the nasopharynx and adjoining structures. Overlying the region of the right pharyngeal tonsil, there was a necrotic hemorrhagic mass about 2 inches in diameter. A zone of necrosis of pharyngeal mucosa surrounded this area. The mass extended posteriorly to involve the right hypoglossal foramen. In a mid-sagittal section going through the sphenoid bone and basilar portion of the occipital bone, it was seen to be entirely extraperiosteal with no evidence of contiguous bone erosion or destruction. The bone marrow in the region of the occipital bone surrounding the foramen magnum was hemorrhagic and necrotic (Fig. 2). This process was seen to continue into the right basilar portion of the occipital bone and for a small area into the petrous portion of the temporal bone. The cortex of the bone was thinned out in areas but at no point was perforated. The dura, arachnoid and brain showed no gross abnormalities.

Microscopic. The soft tissue mass in the nasopharynx was necrotic fibrous tissue, infiltrated with inflammatory cells. There was no tumor present. The adjacent bone showed a diffuse osteomyelitis. There was no evidence of tumor invasion of bone.

DISCUSSION

The sequence of events in this case can be visualized as follows: Following irradiation, an already ulcerated and infected tumor underwent necrosis. The infection reached the adjacent bone marrow, probably through perforating lymphatics. This, added to damage inflicted by irradiation of the bone, resulted in an acute, rather fulminating osteomyelitis with blood stream invasion. The meningeal syndrome was probably a sympathetic meningitis due to the presence of a contiguous suppurative focus and not a bacterial meningitis. The tumor had been completely destroyed by irradiation. Death was directly due to pneumonia.

SUMMARY

A patient with a nasopharyngeal lymphosarcoma presented a meningitis syndrome during the course of roentgen therapy. At postmortem examination this was found to be due to an osteomyelitis of the basilar portion of the occipital bone and not to tumor extension through the base of the skull, as might have been expected.

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EXANTHEM COMPLICATING NEOPLASTIC DISEASE*

ITS IDENTICAL OCCURRENCE IN FOUR CASES OF CARCINOMA

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SKIN reactions are expected locally as a response to roentgen therapy. Generalized skin reactions are unexpected and rare.

Arzt and Fuhs,[1] after treating circumscribed areas of skin, occasionally noted a generalized, rapidly fading, scarlatiniform or fine papular rash associated with pyrexia. This was believed to be a toxic manifestation due to the absorption of cellular decomposition products caused by the roentgen rays. Enfield[2] described a rare roentgen toxic erythema which he thought was unquestionably due to the roentgen ray. He recorded 3 cases in which the rash was generalized, resembled scarlet fever and was accompanied by a febrile reaction lasting several days with temperature as high as 104° F. Pardo Castelló[6] reported 4 cases of disseminated eruptions of the skin occurring after high voltage roentgen therapy. The patients had generalized symptoms consisting of malaise, nausea and vomiting, and slight elevation of temperature. Several days later 2 of the patients showed a morbilliform eruption; one showed disseminated areas of erythema, resembling erythema multiforme, and the other had large edematous papules on the trunk, neck and extremities, resembling the lesions of chickenpox in their initial stage. Subjective sensations were absent except for slight pruritus. The rash disappeared spontaneously except in the erythema multiforme cases where it lasted three weeks and gradually faded. Kautzky[3] stated that exposure to roentgen rays may provoke skin eruptions in patients with hyperthyroidism, psoriasis, and syphilis. He portrayed local reactions in 3 patients and a generalized urticarial reaction in one treated for hyperthyroidism. He thought the reaction might be similar to skin sensitization resulting from barbiturate administration.

MacKee[4] has seen skin reactions of the infectious eczematoid dermatitis type occurring beyond the local area being treated. Uhlmann[11] suggested that a generalized exanthem might develop after irradiation but doubted that such exanthems were caused by the roentgen ray per se. In twelve years of active practice he has never seen a true roentgen exanthem. In all cases coming under his observation, either an accidental concurrent septic exanthem or a suddenly developing erythroderma in psoriasis was demonstrated. He reported a case of a patient receiving radiation therapy to the pelvis for a uterine cancer who developed a scarlatiniform rash from head to feet, with swelling of the eyelids and ankle edema. The patient's condition was poor. A diagnosis of a generalized roentgen exanthem had been made. However, the patient was found to be taking at least eight tablets daily of a barbiturate preparation (optalidon plus sandopta). Four days after this was discontinued the skin reaction regressed. He admitted the possibility of a true roentgen exanthem but believed a summation effect between the barbiturates and the therapy a more plausible cause.

Trostler[9] felt that barbiturates may sensitize the skin to radiation therapy. He stated that many commonly used sedatives such as sulphanol, luminal, and other barbituric acid derivatives produce porphyrinemia and porphyrinuria with resultant sensitization to light and radiation. He saw 3 cases in which severe local reactions, apparently roentgen erythema, occurred. He concluded that the cutaneous response was

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due to the concomitant use of barbiturates. In another communication[10] he referred to Uhlmann's case mentioned above, and pointed out that the barbiturates taken by the patient caused a porphyrinemia and porphyrinuria. He explained the rash on this basis.

However, the porphyrins produce a definite syndrome which has not been demonstrated in Uhlmann's or Trostler's cases. Mason, Courville and Ziskind[5] stated that in every case of hematoporphyria acuta toxica reported up to 1933, the symptoms followed long continued abuse of sulphanol, trianol, and possibly veronal. As a rule, the drug had been taken in daily doses of at least a gram for fully a year before symptoms appeared. Manifestations of the disease have never been reported in acute intoxications with any of these drugs. Kaplan[12] has never observed any rashes similar to those reported by Uhlmann and by Trostler although he has frequently given barbiturates to patients receiving radiation therapy. Richards and Peters[8] and Popp and Binger[7] gave barbiturates in order to diminish radiation sickness. They observed no rashes although other evidences of idiosyncrasy were evident in one patient.

It is difficult to determine from this review of the literature whether a uniform clinical syndrome with a common etiology has been described. Our own experience with 4 essentially similar cases of exanthem occurring after radiation therapy would seem to indicate that we are dealing with a hitherto undescribed entity, having an identical etiology. We present them in order to stimulate further reports and efforts to elucidate the precise causative factors.

REPORT OF CASES

Case 1. A white male, aged sixty, was admitted to the Brooklyn Cancer Institute of the Kings County Hospital on November 11, 1937, with a proved diagnosis of squamous cell carcinoma of the tongue and submaxillary metastases. His family and past history was irrelevant except for asthma of five years' duration. A 3 cm. indurated lesion, surrounded by a few leukoplakic spots, was present on the left side of the tongue. A small hard gland was felt in the left submaxillary region. Physical examination was otherwise negative. The Kline test was negative. Urine examination was normal. Blood count: hemoglobin, 70 per cent; red blood cells, 4.78 million; white blood cells, 5,600, with 76 per cent polymorphonuclears, 24 per cent lymphocytes and no eosinophiles.

On November 18, 1937, ten 2 mg. radium needles were inserted and 2,000 mg-hr. of radium given. On November 26, radiation therapy was started via one anterior, one lateral and one posterior 6×8 cm. portal which included jaw and neck. Two hundred roentgens were given daily through each portal with 200 kv., 20 ma., 50 cm. skin target distance and 2 mm. Cu plus 1 mm. Al filter as factors. On December 8, when he had received 1,600 r anteriorly and posteriorly and 1,800 r laterally, the skin erythema was so severe as to preclude further therapy through these portals. On December 9, intraoral cone therapy was started and patient had received 1,400 r by December 16 when treatment was discontinued.

On December 20, 1937, he complained of stuffed nose, pain in eyes, and pain and burning in mouth. This is taken as the first day of his current illness. On the third day he complained of pain in the throat. On the sixth day his temperature rose to 101.2° and two days later to 102.6° F. He was acutely ill. At this time a generalized erythematopapular rash was noted for the first time. It was present on the neck, trunk, scrotum and extremities, including palms and soles. There was a tender erythema on the face extending beyond the portals exposed to roentgen radiation. The eyelids, bridge of nose and circumoral region were involved. There was a bilateral conjunctivitis. The lesions resembled erysipelas. The mucous membranes of the mouth, throat and nose were extensively involved in a membranous ulcerative process which extended beyond the area treated and was of greater severity than could be expected from a radiation response. Indeed it was so severe as to be thought diphtheritic. His temperature fluctuated irregularly between 99 and 104° F. The face lesions became vesicular, bullous, hemorrhagic and, six days later, crusted. The body lesions became more intense for about three days, remained stationary for a short time and then began slowly to recede. However, the patient continued to be

acutely ill. Blood culture on the twelfth day was negative. Throat cultures taken on the same day showed no diphtheria or Vincent's organisms. *Staphylococcus albus* and *aureus* were present. On the seventeenth day, the throat revealed the same organisms. On the nineteenth day the throat culture showed *Streptococcus anhaemolyticus* and *Staphylococcus albus*. A culture taken from beneath a crusted lesion on the neck showed *Staphylococcus albus* and *aureus* and diphtheroids. Cultures taken from intradermal region of skin lesions were negative. Blood count taken on the eighteenth day showed 3.6 million red blood cells, 11,800 white blood cells, with 42 per cent polymorphonuclears, 2 per cent basophiles, 43 per cent eosinophiles and 13 per cent lymphocytes. Chest roentgenogram taken the same day was negative.

On the twenty-second day of illness, two weeks after their appearance, the face lesions had crusted and fallen off and the skin lesions were almost invisible. Because the patient had been receiving at least a grain and a half of phenobarbital almost daily since admission, this was considered as a possible etiological factor. However, the rash faded although the barbiturates had been continued. The clinical course also spoke against barbiturate poisoning. The patient continued to be critically ill and on the twenty-first day his temperature began to spike, rising to 105° F., on four days. His skin condition had almost entirely disappeared and it was felt that a complication had developed. Blood cultures taken, anaerobically and aerobically, on the twenty-second, twenty-fifth, twenty-sixth and thirty-first days were all negative. Widal test done on the twenty-third day was likewise negative. Urine, negative on the twenty-first day, had occasional white blood cells on the twenty-second day. The blood count on the twenty-fourth day showed hemoglobin, 51 per cent; red blood cells, 3.04 million; white blood cells, 12,650, with 63 per cent polymorphonuclears, 1 per cent basophiles, 18 per cent eosinophiles, 2 per cent monocytes and 16 per cent lymphocytes. Repeat blood count on the thirtieth day disclosed hemoglobin, 53 per cent; red blood cells, 3.15 million; white blood cells, 9,350, with 85 per cent polymorphonuclears, 3 per cent staff cells, 1 per cent eosinophiles, 1 per cent monocytes and 10 per cent lymphocytes. On the thirty-second day his blood chemistry was urea nitrogen 12.72 mg., creatinine 1.5 mg. and sugar 111 mg. per 100 cc. of blood. During the time his temperature was spiking, he developed a cough and became irrational. It was felt that he had bronchopneumonia. In spite of all supportive efforts, including a blood transfusion on the twenty-eighth day, the patient died thirty-five days after onset of illness. Autopsy was not obtained.

Case II. M. C., a white female, aged forty-eight, entered the hospital on December 7, 1937, with a proved diagnosis of transitional cell carcinoma of the pharynx with bilateral cervical gland and possible right petrous bone metastases. Her family and past history was irrelevant. Between August, 1935, and September, 1937, she had received elsewhere a total of 15,400 r with varying factors to various portals about the neck and pharynx, especially on the right. Included, were 1,000 r given intraorally during June, 1937.

Her skin was deeply pigmented over the right cervical region. A 2 cm., hard, fixed gland was found under indurated skin in the region of the lower portion of the sternomastoid. Firm, deep cervical glands were palpable on the left side. The pharynx showed no gross neoplastic masses but contained a large amount of mucus. She had a bilateral horizontal nystagmus and nerve deafness of the right ear. Physical examination was otherwise negative. Her blood count before admission was hemoglobin, 86 per cent; red blood cells, 4.15 million; white blood cells, 5,750, with 68 per cent polymorphonuclears, 32 per cent lymphocytes and no eosinophiles. The Kline test was doubtfully positive. Urine examination on admission showed occasional red blood cells but next day was negative. On December 11, 1937, the right petrous bone was exposed but no metastases were found. She recovered uneventfully except for a herpes labialis.

On January 1, 1938, she complained of nasal congestion, bloody, mucoid nasal discharge and postnasal drip for which ephedrine drops were prescribed. This is called the onset and first day of illness. Between January 3 and 8 she received therapy to her left cervical metastases, through one anterolateral and one posterior portal. Factors were: 200 r daily through 6×8 cm. portal; 200 kv., 20 ma., 50 cm. skin target distance, 2 mm. Cu, 1 mm. Al filter. During this time, 1,200 r had been given through each

portal. The blood count taken on January 4, showed hemoglobin, 60 per cent; red blood cells, 4.05 million; white blood cells, 3,600, with 73 per cent polymorphonuclears, 4 per cent monocytes, and 23 per cent lymphocytes. She complained of headache and nausea. On the sixth day she had a sore throat. On the eighth day she was acutely ill and a patchy, macular dermatitis was noticed on cheeks, nose and lips, well beyond the treated area. The mucous membrane of the mouth, nose and throat resembled a severe Vincent's infection. Next day her temperature rose to 102.8° F. On the eleventh day the face rash had become maculopapular but was limited to face and neck. The left ear was swollen and glazed and resembled erysipelas. The mucous membranes showed oval lesions 1 cm. in diameter, with a gray membranous necrotic surface surrounded by a small area of erythema. No Vincent's organisms were present. Neosalvarsan injections did not improve the condition. Throat cultures revealed *Staphylococcus albus* and *Streptococcus haemolyticus*. Urine examination was negative. Blood count showed hemoglobin, 62 per cent; red blood cells, 3.54 million; white blood cells, 5,000, with 64 per cent polymorphonuclears, 1 per cent staff cells, 2 per cent monocytes, 7 per cent eosinophiles, and 26 per cent lymphocytes. Because the patient had been given between 1½ and 3 grains of phenobarbital almost daily since admission this drug was held responsible and was discontinued. Apparently, however, this did not vary the course of the disease. Her temperature continued to range between 100 and 102° F. By the thirteenth day the face lesion had become confluent. The leukocyte count was 6,500, with 78 per cent polymorphonuclears, 2 per cent monocytes, 5 per cent eosinophiles and 15 per cent lymphocytes. The next day her temperature rose to 103° F. Millet to pea-sized, discrete, sparsely distributed, dark red, maculopapular lesions were noted on the arms, dorsum of hands, abdomen, back and legs. Blood culture was negative aerobically and anerobically. Throat cultures revealed *Staphylococcus albus* and *Streptococcus non-haemolyticus*. Urine showed an occasional leukocyte and red blood cell. The confluent lesions on the face became vesicular on the sixteenth day. Following this they became bullous, hemorrhagic and began to crust two days later. Biopsy of a lesion on the forearm revealed a surface lining epithelium which was histologically normal. The underlying corium presented some edema and a scant perivascular infiltrate of lymphocytes and occasional polymorphonuclears. The lesion was felt to be nonspecific. The leukocytes on that day were 7,950 with 77 per cent polymorphonuclears, 2 per cent monocytes, 2 per cent eosinophiles and 19 per cent lymphocytes. The temperature had begun to recede by lysis. When it rose again from 98° to 101° F. on the nineteenth day, the blood culture was repeated and found negative aerobically and anaerobically. The urine showed an occasional leukocyte and red blood cell. The Kline test was repeated and found negative.

The temperature fell steadily thereafter and by the twenty-third day had been between 98 and 99° F. for two days. The crusts had dried and fallen off the face, the body lesions faded, and the mouth lesions improved. She was discharged on the thirty-second day.

Case III. A. F., white male, aged seventy-eight, with a proved diagnosis of squamous cell carcinoma of the cheek and cervical metastases, was admitted to the Brooklyn Cancer Institute of the Kings County Hospital on February 9, 1938. His family history was irrelevant. His past history included erysipelas of the face thirty-five years prior to admission. His left cheek was indurated externally and disclosed an extensive neoplastic growth internally which covered the entire buccal area. In the left submaxillary region was a marble-sized hard, fixed gland. Physical examination was otherwise negative. Blood count on February 11, 1938, was hemoglobin, 75 per cent; red blood cells, 3.9 million; white blood cells, 9,800, with 70 per cent polymorphonuclears, 2 per cent monocytes, no eosinophiles and 28 per cent lymphocytes. Urine examination was negative. Wassermann and Kline tests were negative.

Between February 10 and March 11, 1938, he received 2,000 r to each of three portals crossfiring the left cheek, as well as one intraoral portal of 2,000 r. The factors previously employed were used here. On March 1, 1938, radiation reaction was first noticed on the mucous membrane and skin. On March 9, the onset day of his present illness, he first complained of soreness, pain in the mouth and sneezing. On March 13 an extensive, generalized, membranous, ulcerative buccal eruption

resembling the two previous cases was seen. His urine showed a 1 plus albumin and an occasional leukocyte and red blood cell. His temperature was 101.6° F. On March 18, the tenth day of his illness, it was noted that the patient developed an erysipeloid eruption, extending considerably beyond the area exposed to radiation therapy. Both sides of his face, especially the left, were involved. He had a bilateral conjunctivitis. His temperature was 101.8° F., and multiple, discrete, small macules, dull red in color, appeared on both forearms and hands and a few on the chest, abdomen and legs. Until the eleventh day of illness he had received, almost daily, small amounts of phenobarbital. This was discontinued but the condition, nevertheless, progressed. The rash on the face progressed similarly to Cases I and II, becoming confluent, vesicular, bullous, hemorrhagic and crusted by the seventeenth day of illness (Figs. 1, 2, and 3). The macules on the arms, chest, back and legs increased in intensity for several days and then gradually receded. There were no Vincent's organisms isolated from the mouth. On the thirteenth day, Wassermann and Kline tests were repeated and found negative. Blood chemistry was normal. His urine on the following day contained 2 plus albumin with an occasional leukocyte and red blood cell.

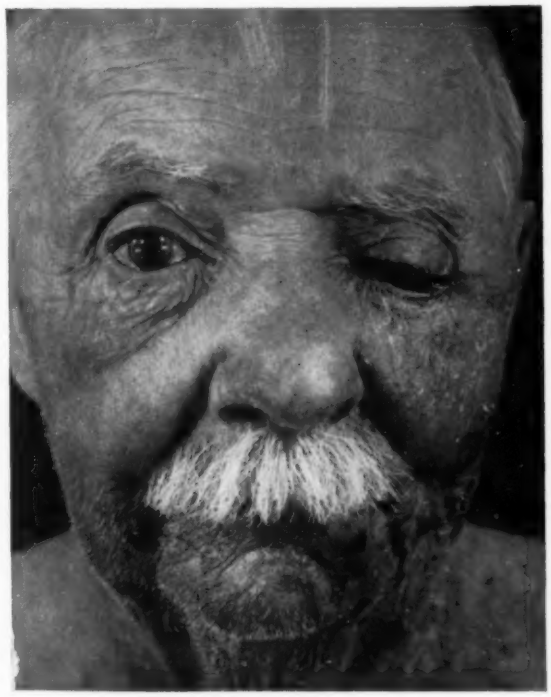

Fig. 1. Case III. Squamous cell carcinoma of buccal aspect of cheek, sixteenth day of exanthem. Note pronounced reaction about eyelids which were not subjected to radiation therapy.

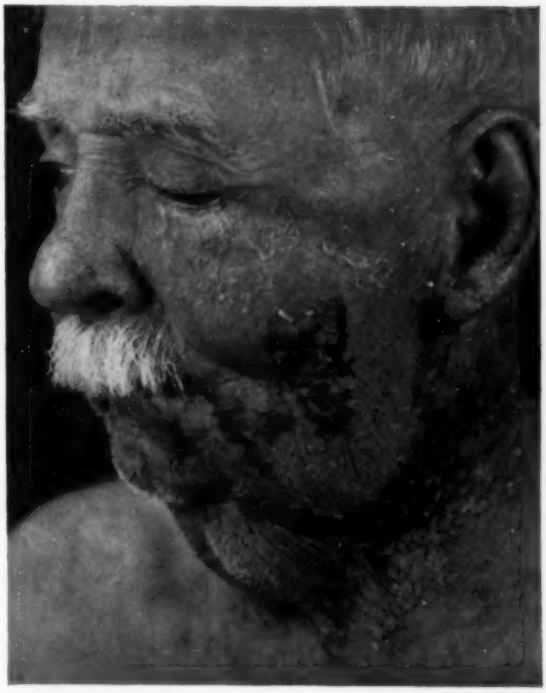

Fig. 2. Case III. Note confluent, vesicular, hemorrhagic, crusted lesion of cheek and glazed appearance of ear.

On the sixteenth day of illness the aerobic and anaerobic blood cultures were negative. *Staphylococcus aureus* and diphtheroid bacteria were isolated from the left side of his mouth and *Staphylococcus albus* and diphtheroids from the right side. Cultures of a cutaneous lesion on the chest yielded *Staphylococcus albus* and *aureus* and *Streptococcus nonhaemolyticus*. Widal examination was negative on the next day. Biopsy of a maculopapule on the right arm was performed and histopathological study showed an intact lining epithelium with a moderately edematous underlying corium and a perivascular lymphocytic infiltration. There was a moderate increase in fixed tissue cells. The diagnosis was nonspecific dermatitis. By the twentieth day of illness the face lesions had crusted and the body lesions had almost completely vanished. The blood count was hemoglobin, 72 per cent; red blood cells, 3.64 million; white blood cells, 10,400,

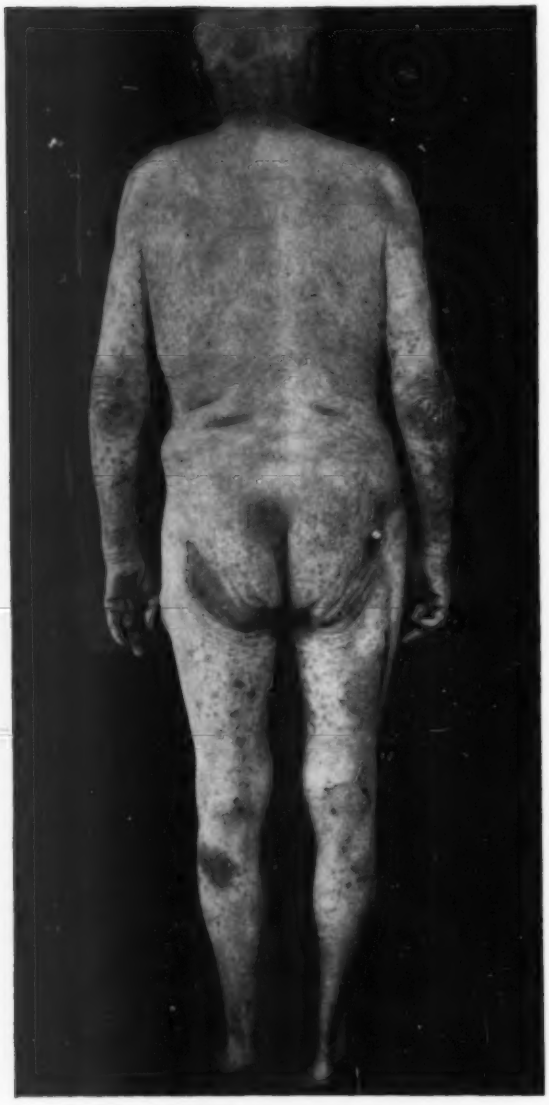

Fig. 3. Case III. The generalized character of maculopapular exanthem is well demonstrated. In areas the lesions have coalesced.

with 72 per cent polymorphonuclears, 1 per cent monocytes, 4 per cent eosinophiles, and 23 per cent lymphocytes. Several lesions on the extremities were severely excoriated due to itching. These became secondarily infected. His temperature fell by lysis concurrently with the fading of his skin lesions and he appeared to be recovering from his initial acute exanthem. However, it so completely exhausted him that he developed a bronchopneumonia to which he succumbed on the twenty-fourth day.

Necropsy by Dr. H. Bolker revealed the following pertinent findings:

Gross: The skin of the left side of the face, ear and neck is discolored purple and covered by fine flaky scales. One area 2×1 cm. on the left cheek is covered by a somewhat thicker brownish scale. The scaling appearance is rather prominent in the folds of the left neck. The ocular conjunctiva on the left is covered by a milky mucoid material. The conjunctival vessels are congested. The cornea shows no changes. The lips, mouth, tongue and pharynx are covered with a dirty mucoid material. In the left buccal mucous membrane is an irregular indurated neoplastic area. On the outer aspect of the left arm 6 cm. above the elbow is an ulcer 2 cm. in diameter which extends through the skin, reaching the underlying muscle; its base is covered by a greenish, necrotic material. There is a reddish area 1 cm. in diameter covered by a fresh crust on the dorsum of the left hand. Several similar areas are found on the right hand, wrist and forearm. There is a suggestion of a macular rash barely visible on the anterior chest wall. Recent excoriations are present on the left chin, one in its mid-portion 3 inches in length and one in its lower third ½ inch in length. A diffuse bronchopneumonic process is present in both lungs. Remainder of gross necropsy findings are irrelevant.

Microscopic examination:

Mouth lesion: A portion of the section is lined by histologically normal stratified squamous epithelium, infiltrated with occasional polymorphonuclear leukocytes. The lining is absent in one area, the base of which is a necrotic, purulent layer. The underlying tissue contains numerous, thin-walled, dilated and congested capillaries, a heavy infiltrate of plasma cells, lymphocytes and polymorphonuclear cells and sheets of invading neoplastic cells of the prickle cell type undergoing degeneration. Numerous small areas of keratinization are definable. There is invasion into the muscular layer, the muscle bundles undergoing degeneration. Large numbers of foreign body giant cells are present in the tumor areas.

Oral mucosa: Sections through the adjacent oral mucosa are lined by epithelium, showing degenerative changes. The underlying tissue is granulation in type.

Skin lesions: All the lesions present a similar picture, more or less marked in different areas. The surface epithelium is undergoing degeneration to varying degree and is covered by a

parakeratotic layer, heavily infiltrated with polymorphonuclear leukocytes. The underlying stroma is edematous, contains numerous, thin-walled, congested capillaries and a leukocytic infiltrate, chiefly perivascular, of the polymorphonuclear and plasma cell varieties. The inflammatory picture is particularly marked in the sections from the left arm, where the deeper layers of the corium and the subcutaneous fatty tissue are the seat of large collections of polymorphonuclear leukocytes, forming localized abscesses. The inflammatory reaction extends into the fatty tissue over wide areas. Similar smaller abscesses are found in the lesions of the left hand. Here the entire epidermis has been replaced by a necrotic layer. Giemsa and Gram stains show the presence of numerous Gram-positive cocci in pairs of short chains in the corium of many of the sections (Figs. 4 and 5).

Lungs: There is moderate subpleural anthracosis. Groups of alveolar spaces have their lumina crowded with polymorphonuclear leukocytes. The corresponding alveolar walls are widened due to capillary congestion. Many of the remaining alveolar spaces are emphysematous. The bronchial lining epithelium is well preserved, the lumina occasionally containing polymorphonuclears.

Case iv. M.S., white female, aged seventy-five, entered the hospital on March 16, 1938, with a proved diagnosis of squamous cell carcinoma of the hard palate. Her family and past history was irrelevant. On the right anterior portion of her hard palate was an ulcerative, hard, neoplastic area with raised edges and a perforation into the maxillary sinus in its midportion. Two firm glands, one marble-sized and the other walnut-sized, were present in the right submaxillary region; a marble-sized one on the left. Physical examination was otherwise negative. Kline and urine examinations were negative.

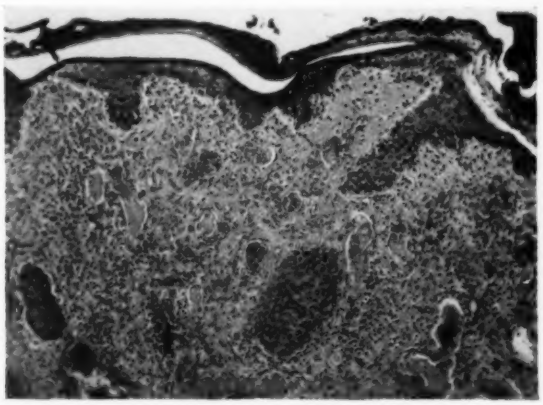

Fig. 4. Case iii. Photomicrograph of section of skin of neck from early lesion showing acute inflammation, edema, vascular congestion, diffuse polymorphonuclear leukocytic infiltrate and parakeratotic layer (×80).

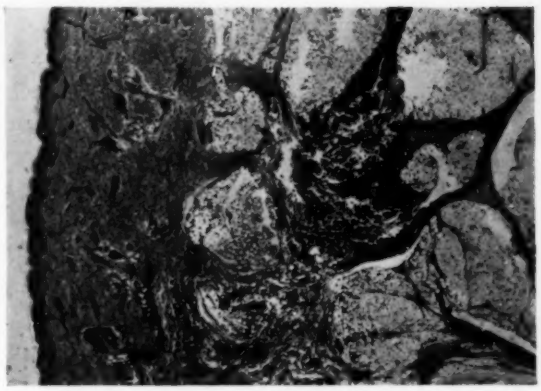

Fig. 5. Case iii. Photomicrograph of section of skin of left arm from a more advanced lesion showing subcutaneous abscess and marked dilatation and congestion of blood vessels in the corium (×12).

On March 18, 1938, roentgen therapy was begun to four portals: a right and left lateral cheek portal, one anterior and one intraoral portal. Factors similar to the previous cases were used. Two hundred roentgens were given daily to each portal rotating right and left. On March 29, 1938, when she had received 800 r to each of the four portals, a pseudomembranous brownish slough of the mucous membranes of the palate and cheeks was noted. Although this was attributed to irradiation, it may well be the onset of the illness under discussion. Her blood count that day was hemoglobin, 92 per cent; red blood cells, 5.2 million; white blood cells, 9,000, with 57 per cent polymorphonuclears, 1 per cent staff cells, 2 per cent monocytes, 12 per cent eosinophiles, and 28 per cent lymphocytes. Her temperature was normal.

On the third day, it rose to 100.2° F. Vincent's organisms were absent from the mouth smears. *Staphylococcus aureus* was present. By the seventh day, her temperature had fallen to normal. Therapy was continued. On the thirteenth day, pea-sized, red, macular areas were noted on the left cheek. The temperature rose to 100.2° F. By then she had received 1,600 r to

all the portals except the left cheek, which received 1,400 r. The next day both cheeks were involved and her temperature rose to 100.8° F. The mucous membranes of the cheeks and lips had small, discrete, pea-sized, oval or round, irregularly-edged, whitish areas surrounded by a deep erythematous base. They appeared at sites apparently beyond the areas exposed to the roentgen ray. Lesions on the face resembled cases seen previously but the severity and generalization were absent. The next day her temperature fell to 99° F. The nurse reported a "prickly heat" type of rash on the back but this faded quickly and was not seen on the eighteenth day when her temperature was 100.2° F. Her temperature fell quickly to normal.

The lesions on the face extended beyond the areas treated but were extremely mild in severity. By the twentieth day they had become confluent and scaling. Her temperature was normal until the twenty-fourth day. Blood count then was hemoglobin, 101 per cent; red blood cells, 4.2 million; white blood cells, 6,000, with 69 per cent polymorphonuclears, 1 per cent monocytes, 1 per cent basophiles, 2 per cent eosinophiles, and 27 per cent lymphocytes. Following the development of a cervical adenitis and rise in temperature to 101° F. for two days, she made an uneventful recovery. By the thirtieth day her facial lesions had entirely faded. She still had small areas in the mouth resembling Vincent's patches. During this entire period she was deemed well enough to continue with her radiation therapy. She received 2,200 r to the intraoral portal, 2,000 r to each of three face portals, 2,000 r to two right neck portals and 2,000 r to two left neck portals. In all she received 16,200 r to her skin via various portals. During her entire stay she received 1½ grains of luminal daily for restlessness and insomnia. She left the hospital improved on July 9, 1938.

DISCUSSION

Of exceptional interest is the fact that the course, pathology, and laboratory data of all 4 cases were so similar as to suggest a distinct clinical entity. All the cases received roentgen therapy in varying amounts about the neck or buccal cavity for carcinoma of tongue, nasopharynx, cheek or hard palate. Coincident with the irradiation or shortly thereafter, all had complaints such as soreness, pain in mouth and sneezing with mucoid bloody discharge. The severity and extent of the reaction could not be explained as a response to roentgen therapy alone, the mucous membranes being involved in areas apparently beyond those exposed to radiation. The face lesions likewise appeared far beyond the area exposed to radiation therapy and could not therefore be ascribed directly to the roentgen ray. In each instance, approximately the same time after the initial complaints, the face lesions appeared; in the first two cases on the eighth day of illness; in the third case, on the tenth day; and in the fourth on the thirteenth day. In the last case as a result of our previous experiences the initial mouth lesions were discovered earlier before subjective symptoms supervened. This may explain the apparently delayed appearance of the face lesions. In all, they first appeared as discrete macules, which became in turn confluent, vesicular, bullous, hemorrhagic, scaled, crusted and dried.

The number of days from appearance to crusting was approximately eight, ten, seven and seven days, respectively. The rashes which appeared on the body were similar. They were first discovered on the eighth, fourteenth, tenth and seventeenth day of illness, respectively. An adequate explanation for the relatively delayed appearance in Case IV has been advanced. All were of a discrete, erythematous, maculopapular type and generally distributed. The skin lesions in the fourth case were evanescent. In the first 3 cases the exanthem lasted approximately nineteen, eleven, and fourteen days, respectively. Coincident with the face and skin lesions the temperature attained high levels and receded by lysis as the rashes faded. Secondary rises in temperature indicated a complication. All the patients were severely toxic. An eosinophilia was common to all. None showed a leukocytosis unless a complication arose. Urine examinations indicated renal disturbance in the first 3 cases.

Blood cultures were invariably negative. Skin and mouth cultures revealed no extraordinary organisms. Intradermal skin cultures of the body lesions were negative in the first case. Biopsy of one of the generalized skin lesions in Cases II and III showed, in each instance, an edematous corium with a perivascular infiltrate of lymphocytes and polymorphonuclear leukocytes. The skin findings at necropsy in the third case were those of secondary infection. Clinically and pathologically the cases resembled each other to a remarkable degree.

An attempt to identify precisely the causative factor or factors would be more or less speculative. Certain clinical entities with which the condition under discussion may be confused can be excluded. Thus, barbiturates were held responsible in some cases previously reported, and suspected to some extent in our own patients. In the previously reported cases the causal relationship is not proved beyond a doubt. Of interest in this connection is the fact that in our Case I the rash receded in spite of the continuance of barbiturates. In Case II the rash progressed despite the discontinuance of the drug. In Case IV, which presented but a mild and evanescent eruption, barbiturates were given over a prolonged period. The exanthems were in all respects similar regardless of barbiturate intake. We have given barbiturates to many patients receiving roentgen therapy, and for long periods of time, without noting a similar reaction. We feel justified in dismissing barbiturate intoxication as a probable primary etiologic factor.

Eczematoid dermatitis, as described by Fordyce, was considered. We have seen several such cases which had their origin in proximity to irradiated areas which were superficially infected or suppurating. These cases bore no resemblance to those under discussion.

Erysipelas had to be ruled out since the face lesions resembled it at one time or another, particularly in the early stages. Case III gave a history of erysipelas thirty-five years previously. The mode of onset, course, generalization of the rash and absence of leukocytosis all spoke against erysipelas. Finally, there was a total lack of response to sulfanilamide therapy. Vincent's organisms were not found in any case. Neoarsphenamine had no effect on the lesions.

The organisms isolated from the mouth were not remarkable, and there is little likelihood that they were the causative factors. One would expect them in any excoriated lesion of the mucous membranes. Diphtheria organisms were never found. The therapy machines used to irradiate these patients were suspected as a possible source of infection. The intraoral cone, the rubber cots used to cover it, and the surface of other cones used were cultured and revealed nothing extraordinary. Other patients treated with the same apparatus during the same period were unaffected.

Undoubtedly the local lesion was due, in part, to the extensive roentgen-ray exposure. In no way, however, could we ascribe the entire picture to the roentgen therapy. Thus, Case IV received 16,400 r about the face and neck with the mildest resultant reaction of the 4 cases reported. Other cases treated similarly showed no generalized response. In every case the rash spread well beyond the area exposed. Finally, the picture did not resemble that of any of the known exanthems.

A generalized skin and systemic reaction was noted. A solution of continuity of skin and mucous membrane was occasioned by tumor formation and aggravated by roentgen therapy. Following irradiation there is a great breakdown of tumor tissue, contiguous normal skin, and mucous membrane. Combined with this is a local vascular disruption. There is thus provided not only an ideal nidus for toxic and infectious agents, but an excellent portal of absorption as well. As a contributory factor the usually weakened condition of the cancer patient undergoing therapy cannot be disregarded.

From the facts available at present, it is impossible to identify precisely the factor or factors responsible for the disorder.

However, several explanations appear plausible. The products of cellular decomposition absorbed into the blood stream may well have caused an allergic or toxic reaction. Indeed such a cytotoxic absorption could hardly be avoided. The eosinophilia, observed in all our cases, suggests such a protein absorption. Similar reactions might be expected wherever radiation reactions were taking place. Skin lesions reported following irradiation of other areas may be rationalized on this basis. If this were actually the case, the gross picture of the toxic response might be the same, but one would expect wide differences in its severity and course depending upon such variables as the amount of cytotoxic substance absorbed. On the other hand, while some cytotoxic absorption must invariably take place following tissue breakdown, generalized reactions, as herein described, are extremely rare. Similarly our first 3 cases were so alike in onset, severity, and day by day course that one must suspect some other mechanism at work. The type of response speaks for a common, constant, causative factor possibly of infectious character. The lowered resistance of the host, the excellent medium for bacterial growth in the broken down tissue, the convenient portal of entry, tend to make this probable. The usual bacteriologic tests revealed primarily the customary non-pathogenic variety of organisms. The rarity of the condition and absence of leukocytosis speak for a bizarre infectious agent, possibly a filterable virus.

We have by no means exhausted all the possibilities but have made a few suggestions regarding the outstanding ones. When one attempts to correlate the maze of uncontrolled and unknown variables, as encountered in such cases, the difficulty of arriving at a direct solution becomes evident. It may well be that some apparently insignificant possibility will assume greater importance when more facts are unearthed or that some combination of factors is responsible. We wish to enlist the interest of other observers in this problem. It is primarily for this reason that these cases are reported.

SUMMARY AND CONCLUSIONS

1. Four cases of a generalized exanthem, apparently associated with localized roentgen irradiation, are reported.

2. The similarity of the four cases is so apparent as to suggest a distinct clinical entity with a common etiology.

3. Barbiturates were administered at some time in each case but evidently played no important rôle in the development of the skin lesions. The exanthems ran their similar course regardless of barbiturate intake.

4. Some additional factors in the causation of this exanthem are discussed.

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Forty-first Annual Meeting: Boston, Mass., October 1–4, 1940.

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Delegates to the Sixth International Congress of Radiology: Albert Soiland, Los Angeles, Calif., Delegate, Zoe A. Johnston, Pittsburgh, Pa., Alternate Delegate.

Twenty-fifth Annual Meeting: Hotel Waldorf Astoria, New York City, June 10–11, 1940.

EDITORIALS

THE CLINICAL ASPECT OF INVOLVEMENT OF THE RETROPERITONEAL LYMPH NODES BY MALIGNANT NEOPLASMS

IN THE spreading of many malignant neoplasms, the lymphatic system as a whole, and the regional lymph nodes in particular, play such an important rôle that the manifestations arising from their involvement often completely dominate the clinical picture. In this respect, the tendency and habits of most metastases, when localized to easily accessible, as for example, the cervical, axillary or inguinal, lymph node groups are thoroughly understood. The symptoms and physical signs are as a rule found to be so well correlated with the degree of pathologic extension that one could almost speak, if it were not for the self-evident simplicity, of veritable syndromes. Even the mediastinal lymph nodes, thanks to the manifold and exacting roentgenologic methods at our disposal today, can now be easily investigated, and their invasion, either by secondary or primary neoplasms, constitutes an open problem, in most instances comparatively easy of solution. Curiously, however, little attention has been paid to the retroperitoneal lymph nodes, although because of their vast ramifications and extensive connection with organs which may form the site of many tumors, they represent perhaps the most important regional group of lymph nodes in the body.

Recently Desjardins,* in an exhaustive article, published some very interesting observations on the clinical aspect of involvement of the retroperitoneal lymph nodes by malignant neoplasms. His study was based on the wealth of material at the Mayo Clinic. In a personal communication he states that in the lymphoblastoma alone the histories and case reports of not less than two thousand cases treated since 1920 were analyzed. The compilations extended over a period of nearly four years, and, therefore, considering the meticulously careful investigative nature and the arduous solicitude for the unbiased truth of the author, the results arrived at may be considered as of the utmost practical significance.

Anatomically, the retroperitoneal lymph nodes in a broader sense include the two main groups of the iliac and abdomino-aortic nodes, with these latter again divided into the mesenteric and para-aortic nodes. All of them are connected by lymph channels with each other and with the individual organs. It is noteworthy that the lymph from every abdominal or pelvic organ, as well as from the lower extremities, must drain through the para-aortic or through both the mesenteric and para-aortic nodes to reach the thoracic duct and hence the left subclavian vein. A smaller amount of lymph passes into the vessels which form an anastomosis between the upper para-aortic nodes and those following the upward course of the aorta on the left side and of the inferior vena cava on the right. It must also be mentioned that the upper para-aortic nodes constitute a direct receptacle for the lymph coming in separate channels along the spermatic and ovarian arteries from the testes or ovaries, a fact which explains why malignant tumors of these organs, unless the capsule has been ruptured, first metastasize to the high abdominal lymph nodes and not to

* Desjardins, Arthur U. Retroperitoneal lymph nodes; their importance in cases of malignant tumors. *Arch. Surg.*, 1939, *38*, 714-754.

the topographically closer inguinal nodes as might be supposed.

Paying due regard to these peculiarities of anatomic distribution, Desjardins distinguishes in the main three clinical forms of involvement of the retroperitoneal lymph nodes, such as metastasis from carcinoma of most pelvic organs, metastasis from tumors of the testis and ovary, and lymphoblastomatous invasion.

Metastasis from Carcinoma of Pelvic Organs. The most common organs concerned are the bladder, prostate gland, uterus and rectum. If a carcinoma originating from any of these organs spreads to the retroperitoneal lymph nodes, the chief clinical symptoms may be summed up as follows: backache, which affects mostly the lumbar region, is of a dull character and is at times relieved following roentgen irradiation; pain in the abdomen, manifesting itself either in the form of irregular attacks or of more or less regular spells occurring after meals and thus suggesting peptic ulcer; bloating and belching, usually associated with a sensation of fullness in the epigastrium after eating and in later stages with crowding of the stomach; gradually developing enlargement of the abdomen and finally persistent severe constipation. The physical signs, if not overshadowed by those of the primary neoplasm or its extension to some other abdominal organ, as, for example, the liver, consist principally of the presence of an abnormal, deep-seated resistance in the epigastric or umbilical region and the complaint by the patient of a slight or moderate tenderness when pressure is exerted on this resistance.

Metastasis from Malignant Tumors of the Testis or Ovary. By far the most frequent neoplasms of the testis are the seminoma and the teratoid tumor, both types of which metastasize, according to Desjardins, much earlier than is generally suspected. As already stated, the first metastasis is almost always in the para-aortic lymph nodes, as a rule above the point of entry of the spermatic artery. Only after the tumor has broken through the capsule of the testis is there an extension to the inguinal lymph nodes. In many instances, efficient blockage by the retroperitoneal nodes may delay further spreading of the malignant process for many months or even years. A similar situation may occur in malignant neoplasms of the ovary, although here the more rapid perforation of the capsule often changes the mode of dissemination.

The clinical symptoms in connection with metastasis to the retroperitoneal lymph nodes of the malignant tumors of the testis or ovary are identical with those described for metastasis of carcinoma of other pelvic organs. Likewise the physical signs are the same, except perhaps for the fact that the mass or resistance which is felt in the upper abdomen is more apt to be situated to the right or left of the midline, according to which side was primarily affected. Rarely there may also be retrograde extension to the iliac nodes when the malignant cells are "dammed back" by the blocking of the para-aortic lymph nodes as demonstrated in the experiments of Jamieson and Dobson.* In malignant neoplasms of the ovary with early perforation of the capsule, the clinical picture is obscured by the signs of peritoneal dissemination such as ascites, meteorism, etc., so that a diagnosis of retroperitoneal involvement often appears difficult or impossible.

Lymphoblastoma (Hodgkin's Disease or Lymphosarcoma). It is in Hodgkin's disease and lymphosarcoma that the involvement of the retroperitoneal lymph nodes assumes the greatest clinical importance. Whether the neoplastic invasion occurs primarily or is the result of secondary extension from the cervical, mediastinal or some other lymph node groups, it invariably gives rise to symptoms or signs which sooner or later become predominant. Desjardins considers the following features as being indicative or at least suggestive of affection of the retroperitoneal lymph nodes by lymphoblastoma:

* Jamieson, J. K. and Dobson, J. F. The lymphatics of the testicle. *Lancet*, 1910, *1*, 493-495.

The symptoms often vary in degree from time to time and following the most varied kinds of treatment as, for example, even an erroneously performed appendectomy or cholecystectomy, they may undergo complete remission for a shorter or longer period. Their rapid deterioration, as a rule, signifies that the lymphoblastoma has invaded the structures of the throat, the mediastinum, the hemopoietic system or the retroperitoneal lymph nodes, with the latter leading in point of frequency as well as relative importance.

Individually, the most outstanding symptoms in connection with the involvement of the retroperitoneal lymph nodes by the lymphoblastoma are: the loss of strength; the unaccountable and often extremely rapid loss of weight; the slowly but more or less steadily increasing upper abdominal discomfort or pain in contradistinction to the painlessness of lymphoblastoma of other locations; the likewise continuously increasing backache; the bloating and belching, usually greatest after eating, and sometimes associated with nausea or vomiting; the fever, which is of the Pel-Ebstein or the continuous variety, and which, more than anything else, indicates retroperitoneal (or more rarely mediastinal) invasion; and finally the pruritus which, like the fever, constitutes another positive sign.

Of the less frequent, and not altogether characteristic, symptoms one may mention the increased pigmentation of the skin, the constipation, the edema, the ascites, the jaundice and the secondary urinary disturbances.

The physical signs, according to Desjardins, are few. Moreover, they are entirely missing in the earlier stages of the involvement even in instances in which the clinical symptomatology is fully developed. Only after the lymph nodes have enlarged to a considerable size is it possible to elicit the first tangible physical evidence either in the form of solitary tumors when the nodes are individually affected, or of a deep resistance when they are packed together or matted to the adjacent structures. The other worthwhile physical sign is tenderness on pressure which in most cases is quite definite, although not always unmistakable.

Roentgen examination also has a very limited usefulness. Occasionally the demonstration of a filling defect in the stomach, small intestine or colon on gastrointestinal study or of a dilated ureter and kidney pelvis on urography permits the supposition of extrinsic pressure effect, but the source as a rule remains undetermined.

Taken as a whole, it becomes evident that a knowledge of the clinical picture of the involvement of the retroperitoneal lymph nodes by malignant neoplasms is of great practical significance. Many times the array of potential symptoms may appear too long and the corresponding number of actual physical signs too small to permit an entirely lucid interpretation; nevertheless the continuous remembrance of the various possibilities will help in establishing more rational and certainly more circumspective therapeutic criteria. It thus will seem by no means unjustified to extend irradiation in all the above enumerated neoplastic conditions to the retroperitoneal lymph nodes whenever there is the slightest clinical suspicion that they may be affected or, even prophylactically, whenever there is a chance that their invasion may be reasonably prevented. On such a basis one will not hesitate, for example, to administer radiation therapy routinely to the upper abdomen in addition to other customary regions in all cases of malignant tumors of the ovary and especially the testis. Moreover, in lymphoblastoma a similar procedure, when leading to remission of unaccountable clinical symptoms such as fever, pruritus, loss of weight, etc., acquires the significance of a true differential test, both as to the probable nature and definite location of the active pathologic involvement.

T. Leucutia

AMÉDÉE GRANGER
1879—1939

DR. AMÉDÉE GRANGER, internationally famous radiologist and head of the radiological department of the Charity Hospital in New Orleans, died December 15, 1939, from a heart attack.

A native of New Orleans, Dr. Granger at the time of his death was a faculty member of the Louisiana State University Medical Center and head of the department of roentgenology at Charity Hospital, a position he had held since its creation in 1905. Dr. Granger was for many years a member of the Tulane University Medical faculty, but he became affiliated with Louisiana State University in 1931.

Famed particularly for his development of the sinus position which bears his name under the caption of the "G-line," Dr. Granger perfected many other ingenious devices for use in the roentgen examination. During the World War he was decorated by the French Government for his development of a machine to localize bullets by the aid of the roentgen ray. On other occasions he was the recipient of honors from the governments of France, Belgium and Italy.

Dr. Granger was born in New Orleans in 1879 and received his early education in private school and at the Boys' High School in New Orleans. He later attended Tulane University and was graduated from the Medical School in 1901. His study at Tulane was interrupted when he was mustered into service in the war with Spain in 1898 to serve in the Hospital Corps. In 1905, when he was appointed to organize the department of roentgenology at Charity Hospital, he was given only 169 square feet of space and one orderly. Nevertheless, he made over nine hundred roentgenograms the first year and through his guidance, this department at Charity Hospital is now one of the largest and best equipped in the country.

Dr. Granger's accomplishments were widely recognized abroad. King Albert of Belgium, through the Belgian Consul in New Orleans, made him a Knight of the Order of the Crown in 1929. In 1930, he was paid the same honor by King Victor Emanuel of Italy. In 1934, he was received into the membership of the Legion of

Amédée Granger

Honor of France. He had previously been awarded the silver and gold "Palmes Universitaires."

A past first vice-president of the Radiological Society of North America, Dr. Granger was awarded the Society's gold medal in 1926 in recognition of his achievements. He held membership in many other medical and scientific societies. He was a charter member and past chancellor of the

American College of Radiology; past vice-president of the French-speaking Physicians of North America; past president of the Orleans Parish Medical Society; honorary member of the Texas Radiological Society; honorary member of the New Orleans Ophthalmological Oto-laryngological Society; collaborator of *Radiology;* and an honorary member of the Alpha Omega Alpha medical fraternity.

Dr. Granger made many contributions to the science of radiology. The development of roentgen treatment for acute mastoiditis in children, before the softening and breaking down of bone, was the one of which he was most proud. The board of administrators of Charity Hospital gave a reception in his honor when, in 1930, he first presented a paper on this form of treatment. This was the first time in the history of the Hospital that such an honor had been tendered a member of the Hospital staff. The devising of contrivances for improving roentgenological technique was indeed his hobby. His laboratory was filled with ingenious devices which he used for his own convenience.

Dr. Granger is survived by his wife, Corinne Pruitt Granger, whom he married in 1917, and two sons by a former marriage, Amédée, Jr., and Carroll.

He will be greatly missed in New Orleans and by the whole country. As a gentleman of extensive culture and refinement and as an acknowledged and honored scientist, he was beloved by his associates and his many friends.

Ernest Charles Samuel

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer.

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. B. Peirce, Royal Victoria Hospital, Montreal, Canada. Annual Meeting: Hotel Statler, Boston, Mass., Oct. 1–4, 1940.

American College of Radiology
Secretary, Mac F. Cahal, 540 N. Michigan Ave., Chicago, Ill. Next Annual Meeting: Commodore Hotel, New York City, June 12, 1940.

Section on Radiology, American Medical Association
Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: New York City, June 10–14, 1940.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting, 1940: To be announced.

Radiological Section, Baltimore City Medical Society
Secretary, Dr. Walter L. Kilby, Baltimore. Meets third Tuesday each month, September to May.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets twice annually in May and September.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill. Next meeting, Peoria, Ill., May 21–23, 1940.

Radiological Section, Los Angeles Co. Med. Soc.
Secretary, Dr. Wilbur Bailey, 2007 Wilshire Blvd., Los Angeles, Calif. Meets on second Wednesday of each month at County Society Building.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Brooklyn Roentgen Ray Society
Secretary, Dr. L. J. Taormina, 1093 Gates Ave., Brooklyn, N. Y. Meets monthly on first Tuesday, October to April.

Buffalo Radiological Society
Secretary-Treasurer, Dr. Joseph S. Gian-Franceschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months, place of meeting selected by the host.

Chicago Roentgen Society
Secretary, Dr. C. J. Challenger, 3117 Logan Blvd. Meets second Thursday of each month October to May inclusive at the Hotel Sherman.

Cincinnati Radiological Society
Secretary, Dr. J. E. McCarthy, 707 Race St., Cincinnati, Ohio. Meets third Tuesday of each month, October to May, inclusive.

Cleveland Radiological Society
Secretary, Dr. H. A. Mahrer, 10515 Carnegie Ave. Meets at 6:30 P.M. at Mid-Day Club rooms on fourth Monday each month, October to April, inclusive.

Denver Radiological Club
Secretary, Dr. P. R. Weeks, 520 Republic Bldg., Denver, Colo. Meets third Friday of each month.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

Florida State Radiological Society
Secretary, Dr. J. N. Moore, 210 Professional Bldg., Ocala, Florida. Meetings in May and November.

Georgia Radiological Society
Secretary, Dr. R. C. Pendergrass, Prather Clinic Bldg., Americus, Ga. Meets in November and at annual meeting of Medical Association of Georgia in the spring.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meetings held quarterly, on the fourth Sunday of the month.

Indiana Roentgen Society
Secretary, Dr. C. C. Taylor, 23 E. Ohio St., Indianapolis, Ind. Meeting held the second Sunday in May annually.

Kentucky Radiological Society
Secretary, Dr. J. C. Bell, 402 Heyburn Bldg., Louisville. Meets annually in Louisville on third Sunday afternoon in April.

Long Island Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

Michigan Association of Roentgenologists
Secretary, Dr. C. S. Davenport, St. Lawrence Hospital, Lansing. Three meetings a year, Fall, Winter, Spring.

Milwaukee Roentgen Ray Society
Secretary, Dr. I. I. Cowan, Mt. Sinai Hospital, Milwaukee, Wis. Meets monthly on first Friday at University Club.

Minnesota Radiological Society
Secretary, Dr. J. P. Medelman, 572 Lowry Medical Arts Bldg., St. Paul.

Nebraska Radiological Society
Secretary, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets third Wednesday of each month, at 6 P.M., at either Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. A. O. Hampton, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

Radiological Society of New Jersey
Secretary, Dr. W. J. Marquis, 198 Clinton Ave., Newark. Meets annually at time and place of State Medical Society. Mid-year meetings at place designated by president.

New York Roentgen Society
Secretary, Dr. R. D. Duckworth, 170 Maple Ave., White Plains, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

North Carolina Roentgen Ray Society
Secretary, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

Central New York Roentgen Ray Society
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year—January, May, November.

Pacific Roentgen Club
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. L. E. Wurster, 416 Pine St., Williamsport, Pa. Next annual meeting, Hershey Hotel, Hershey, Pa., May 17–18, 1940.

Philadelphia Roentgen Ray Society
Secretary, Dr. B. R. Young, Temple University Hospital. Meeting first Thursday of each month from October to May inclusive, at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St.

Pittsburgh Roentgen Society
Secretary, Dr. H. W. Jacox, 4800 Friendship Ave., Meetings held second Wednesday each month, 4:30 P.M., October to June at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. S. C. Davidson, 277 Alexander St. Meets on second Thursday from October to May, inclusive, 8 P.M., Rochester Academy of Medicine Building.

St. Louis Society of Radiologists
Secretary, Dr. W. K. Mueller, University Club Bldg. Meets fourth Wednesday of October, January, March and May, at a place designated by the president.

San Francisco Radiological Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco. Meets monthly on first Monday at 7:45 P.M., alternately at Toland Hall and Lane Hall.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

South Carolina X-Ray Society
Secretary, Dr. Hillyer Rudisill, Jr., Roper Hospital, Charleston. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. F. B. Bogart, 311 Medical Arts Bldg. Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. L. W. Baird, Scott and White Hospital, Temple, Texas. Next annual meeting, January 18, 1941, Sherman, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 p.m. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 p.m., Room 301, Service Memorial Institute.

Virginia Radiological Society
Secretary, Dr. V. W. Archer, University Hospital, University, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. K. J. Holtz, American Bank Bldg., Seattle. Meets fourth Monday of each month at the College Club, Seattle.

Cuba

Sociedad Cubana de Radiologia y Fisioterapia
Secretary, Dr. Francisco Padron, Enrique, Villuendas 64, Havana, Cuba. Meets monthly in Havana.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets monthly on third Thursday, from November to June inclusive, at 8:15 p.m., 32 Welbeck St., London.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 p.m. at the Royal Society of Medicine, 1, Wimpole St., London, W. 1.

Faculty of Radiologists
Secretary, Dr. Barbara M. Key, 32 Welbeck St., London, W. 1, England.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to November inclusive for scientific discussion.

Canadian Association of Radiologists
Secretary, Dr. A. C. Singleton, Medical Arts Bldg., Toronto, 5, Ontario.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext., Halifax, N.S.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

Continental Europe

Belgian Society of Roentgenology
Secretary, Dr. J. Boine, Avenue des Alliés, 134, Louvain (Belgium). Meets monthly on second Sunday at d'Egmonds Palace, Brussels, except in the summertime.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Société de Radiologie Médicale de France
Meets monthly on second Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. A. Grosjean, La Chaux de Fonds.
Secretary for German language, Dr. Scheurer, Molzgasse, Biel. Meets annually in different cities.

Société Francaise d'Electrothérapie et de Radiologie Médicale
Meets monthly on fourth Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Association of German Roentgenologists and Radiologists in Czecho-Slovakia
Secretary, Dr. Walter Altschul, German University, Prague, 11.52.

Deutsche Röntgen-Gesellschaft (Gesellschaft für Röntgenkunde und Strahlenforschung)
Meets annually in April, alternating one year in Berlin, one year in some other German city. Meets in addition every two years with the Gesellschaft deutscher Naturforscher und Aerzte.
Permanent Secretary, Professor Dr. Haenisch, Klopstockstrasse 10, Hamburg, Germany.

Süd- und Westdeutsche Röntgengesellschaft
Meets annually in different cities.

Nord- und Ostdeutsche Röntgengesellschaft
Meets annually in different cities.

Dutch Society of Electrology and Roentgenology
Holds two meetings a year in Amsterdam, one in the spring, and one in the fall.

Societa Italiana Radiologia Medica
Secretary, M. Ponzio, University of Turin, Prof. Turin

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banul Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad, USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly on first Monday at 8 o'clock.

Polish Society of Radiology
Secretary, Dr. Jan Kochanowski, 45 Gornoslazka St., Warsaw. Meets annually.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. B. Krynski, 11 Zielna St. Meets once a month except in the summertime.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association. Each of the following societies, with exception of the Denmark Society, meets every second month except in the summertime:

Society of Medical Radiology in Sweden
Meets in Stockholm.

Society of Medical Radiology in Norway
Meets in Oslo.

Society of Medical Radiology in Denmark
Secretary, Dr. G. Biering, Copenhagen. Meets the second Wednesday of each month from October to July in Copenhagen, at 8 'oclock in the State Institute of Roentgenology.

Society of Medical Radiology in Finland
Meets in Helsingfors.

Vienna Roentgen Society
Meets first Wednesday of each month, at 6:30 p.m. at Zentral-Röntgen Institut des allgemeinen Krankenhauses Alserstrasse 4.

Orient

Japan X-Ray Association
c/o Orthopedic Surgery, Tokyo Imperial University. Meets annually in April.

Kinki Roentgen-Abend Society
Director, Dr. Prof. Taiga Saito, Ogawaoike Tyoto Japan. Meets bi-monthly on third Sunday.

AMERICAN COLLEGE OF RADIOLOGY ANNOUNCES PROFESSIONAL BUREAU

In 1937 the American College of Radiology started operation of a placement bureau in an effort to bring together those radiologists who were looking for locations and those hospitals and medical groups who were seeking radiologists. This bureau was started as an experimental venture in order to determine whether or not there was need for such a service. During the experimental period very little publicity was given to the availability of such a service, but even without publicity the placement bureau has been able to offer its facilities to approximately seventy applicants and institutions. Likewise, it has aided individual radiologists who sought a well trained associate to take care of an expanding practice.

Prior to the establishment of the placement bureau it had been the custom of hospitals to write to a few medical centers which were training radiologists and ask if any well trained man was available. If none was obtainable they were forced to consult one institution after another until a satisfactory man was found. Another source of obtaining radiologists was through the commercial bureaus.

At the recent annual meeting of the Board of Chancellors of the American College of Radiology it was deemed advisable to expand the activities of the placement bureau and make it a truly Professional Bureau. At the present time a full biography including college and medical training, period of interneship, and residency, is being compiled for all applicants. Each hospital, or group, or individual requesting a radiologist is asked to furnish detailed information pertaining to the nature of the practice. If a hospital, it is queried concerning size, population of the community, equipment, and other pertinent facts about its radiological department.

The applicants are requested to state whether or not they are diplomates of the Board of Radiology and to specify their period of training in order that it may be determined whether or not they are to be potential candidates for the Board examinations. The Professional Bureau accepts as applicants only those who have had sufficient training to be candidates for the Board or those who have been awarded certificates by the Board. (The Bureau does not undertake to place residents or to find locations for those men desiring to enter training; nor does it endeavor to furnish technicians.)

At the present time there are eighty-eight approved radiological centers training one or more men. It is the plan that when a request is received all applicants and the chief of the department in which each man received his training will be notified of the opening. The men are requested to write to the individual or institution for further information and also to furnish the credentials requested. This method of procedure is followed because of the fact that each opening calls for different requirements and by going over the credentials of the applicants the inquirers can select those whom they feel meet their particular needs. The Professional Bureau acts in an advisory capacity between the institution and the applicant and intends to make every attempt to obtain the additional information necessary for each party.

Up to the present time no charge has been made to either applicant or hospital for services rendered. It is evident that the expense to be incurred by the College in the operation of such a Professional Bureau is rather difficult to estimate at the present time, and all expenses are now being borne by the College. It has been decided that if and when the operation of the Bureau is sufficiently large to incur considerable expense from which only the applicants will benefit, then a small registration charge will be made.

All hospitals, groups, clinics, and individuals, seeking the service of a radiologist or an assistant in the radiological de-

partment are invited to communicate with Dr. S. W. Donaldson, Director of the Professional Bureau, American College of Radiology, 540 North Michigan Avenue, Chicago.

AMERICAN RADIUM SOCIETY

The Twenty-fifth Annual Meeting of the American Radium Society will be held in New York City on Monday and Tuesday, June 10 and 11, 1940, at the Hotel Waldorf Astoria.

The Janeway Lecture will be given by Dr. Edith H. Quimby on Monday afternoon at four o'clock on the subject "The Specification of Dosage in Radium Therapy." Formal presentation of the Janeway Medal will be made at the dinner on the evening of the same day.

A clinical demonstration at Memorial Hospital has been arranged for Wednesday afternoon, June 12, and a visit to the cyclotron at Columbia on Thursday afternoon, June 13, to avoid conflict with the Section on Radiology of the American Medical Association which will be in session during the mornings on these days. Members who have not obtained hotel reservations should do so promptly.

EIGHTH AMERICAN SCIENTIFIC CONGRESS

The Department of State announces that the Eighth American Scientific Congress will be held in Washington, D. C., from May 10 to 18, 1940, under the auspices of the Government of the United States.

Pursuant to a special act of the Congress of the United States invitations on behalf of the President have been extended to the Governments of the American Republics members of the Pan American Union to participate in the forthcoming meeting. Scientific institutions and organizations are also cordially invited to send representatives.

On April 14, 1940, the Pan American Union will celebrate the fiftieth anniversary of its founding. Although the Eighth American Scientific Congress will convene a few weeks subsequent to the anniversary date, the Congress will be one of the important phases of that notable celebration.

The Congress will be divided into the following sections, each to be in charge of a chairman assisted by a vice chairman, secretary and section committee: anthropological sciences; biological sciences; geological sciences; agriculture and conservation; public health and medicine; physical and chemical sciences; statistics; history and geography; international law, public law and jurisprudence; economics and sociology; education.

The official languages of the Congress will be English, Spanish, Portuguese and French. Papers may be submitted in any one of the official languages and appropriate arrangements will be made for the presentation of these papers, or résumés thereof, in the other official languages.

The Honorable Cordell Hull, Secretary of State, has requested the following government officials and distinguished scientists to serve upon an Organizing Committee which is collaborating with the Department of State in formulating definite plans for the Congress:

The Honorable Sumner Welles, Under Secreary of State, *Chairman.*

Dr. Warren Kelchner, Acting Chief, Division of International Conferences, Department of State, *Vice Chairman.*

Dr. Alexander Wetmore, Assistant Secretary of the Smithsonian Institution, *Secretary* and *Secretary General of the Congress.*

Dr. C. G. Abbot, Secretary of the Smithsonian Institution.

Dr. Isaiah Bowman, President, John Hopkins University.

Dr. Vannevar Bush, President, Carnegie Institution of Washington.

Dr. Ben M. Cherrington, Chief, Division of Cultural Relations, Department of State.

Mr. Laurence Duggan, Chief, Division of the American Republics, Department of State.

Dr. Ross G. Harrison, Chairman, National Research Council.

Dr. Waldo G. Leland, Secretary, American Council of Learned Societies.

Mr. Archibald MacLeish, Librarian of Congress.
Dr. Thomas Parran, Surgeon General, United States Public Health Service.
Dr. Stuart A. Rice, Chairman of the Central Statistical Board.
Dr. Leo S. Rowe, Director General, Pan American Union.
Dr. James Brown Scott, Trustee and Secretary, Carnegie Endowment for International Peace.

RED CROSS TO ENROLL MEDICAL TECHNOLOGISTS

At the request of the Surgeon General of the Army and in compliance with its policy of cooperation with both the Army and Navy, the American Red Cross, as an expansion of its peace-time service for the military forces, has undertaken the enrollment of various types of medical technologists who are willing to serve in the medical department of the Army and Navy if and when their services are required at the time of a national emergency.

Persons with the following qualifications will be enrolled:

Chemical laboratory technicians (male)
Dental hygienists (male and female)
Dental mechanics (male)
Dietitians (male and female)
Laboratory technicians (male and female)
Meat and dairy hygienists (inspectors) (male)
*Nurses (male)
Occupational therapy aides (male and female)
Orthopedic mechanics (male)
Pharmacists (male and female)
Physical therapy technicians (aides) (male and female)
Statistical clerks (male and female)
X-Ray technicians (male and female)

General qualifications for enrollment are as follows:

1. Citizens of the United States.
2. Ages 21–45 years (Army); 18–35 (Navy—*men only*)
3. Physically qualified. Applicants must pass a satisfactory physical examination, according to standards set respectively by the Army and Navy Medical Departments.
4. Women applicants must be unmarried.
5. All applicants must express a willingness to serve as a technologist in time of a national emergency.

Male technologists will be eligible for enlistment in the Army as non-commissioned officers in the grades of sergeant, staff sergeant, or technical sergeant. Women technologists, and men who do not qualify physically, will be eligible for employment by the Army as civilians.

For the Navy, male technologists will be eligible for enlistment in the Naval Reserve as Petty Officers—Pharmacist's Mates 3d, 2nd, and 1st Class and Chief Pharmacist's Mate (acting appointment). Women technologists are not eligible for service in the Navy under present plans.

The Medical Department of the Army will require a considerable number of technologists in each of the above named groups. The Navy Medical Department requirements will be similar except for dietitians, occupational therapy aides, orthopedic mechanics and dairy and food hygienists (inspectors) who will not be needed. Notwithstanding the maintenance of this enrollment, the Navy also desires peace-time enlistment in the U. S. Naval Reserve, and male technologists who wish to enlist in the Naval Reserve are urged to communicate direct with the Commandant of the Naval District in which they reside. The address of their Commandant will be furnished upon request.

Technologists who qualify according to these general standards and who are willing to enroll for service as outlined above should communicate with the American National Red Cross, Washington, D. C.

* This group will not be members of the Army or Navy Nurse Corps which under basic law are limited to females, but will be used as technologists for service auxiliary thereto.

CALCIFICATIONS IN THE SPLENIC REGION

To the Editor:

A short time ago I had the occasion to recheck some of the autopsy material used in the preparation of my paper (Calcifications in the Splenic Region. Am. J. Roentgenol. & Rad. Therapy, June, 1939, *41*, 931–949) in collaboration with several

members of the Department of Pathology at Mt. Sinai Hospital, New York City.

Three cases of splenic phleboliths were originally found in the autopsy protocols of the above mentioned hospital and reported as such in the article. Careful microscopic re-examination of representative sections of two of these spleens failed to demonstrate the calcific bodies lying in or intimately connected with blood vessels. In the third case histological study of the splenic calcification was not made.

Therefore, in the interests of accuracy, I should like to alter the position of the three cases originally presented as splenic phleboliths to that of calcifications of undetermined origin.

Arnold L. Bachman

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers as space permits.

Chronic Arthritis in Wild Mammals. By Herbert Fox, Professor of Comparative Pathology, University of Pennsylvania; Director, William Pepper Laboratory, Hospital of the University of Pennsylvania. Transactions of the American Philosophical Society Held at Philadelphia for Promoting Useful Knowledge. New Series—Volume XXXI, Part II. Paper, $2.00, per volume. Pp. 73–149, with numerous illustrations. Philadelphia: The American Philosophical Society, 1939.

This monograph is an analysis of more than seventeen hundred skeletons and autopsies of wild animals of which some revealed changes in the joints that correspond with those of chronic arthritis in man. The material was obtained from the autopsy service at the Zoological Garden, Philadelphia, from museums and from wild animals which were killed by naturalists on expeditions and by hunters. In 1,749 skeletons, 77 cases of arthritis were found.

The introduction to the monograph contains a statement of the intention and the plan of the work, a description of the sources of the material, a definition of arthritis as applied to wild animals and a discussion of the limitation of the material and of the value of roentgen examination of the bones. Following this is a table which lists the skeletons of the animals and the autopsies performed on them, arranged according to zoological classification with common names of the principal examples. The anatomical characteristics of the articular changes in each class are fully described in tabulated form. In the concluding paragraphs the ecology and habits of the various groups, the associated morbid states and the relationship of diet, age and body bulk to arthritis are discussed.

The illustrations are profuse and are very clear with excellent detail of both autopsy specimens and roentgenograms. The latter were submitted to trained roentgenologists and the readings which are given are in accord with their interpretations. Evidences of hyperostotic overgrowth, osseous solidifications, porosis and surface defects which are present, are comparable to those observed in roentgen examination of human joints. Dr. Fox believes that chronic arthritis can be well demonstrated in wild animals by roentgen examination and the findings which are obtained amplify and support the interpretations of the gross specimens by the pathologist.

Arthritis was best seen as an involvement of the spinal column but it also occurred very extensively in the appendicular skeleton. The distributions of the lesions in different kinds of animals suggested that a relationship may exist between function and localization of disease. Thus locomotion and the jolt shock associated with it may be a factor in its production. Macrosomic animals were found to be conspicuously affected; small bodied animals, rodents, bats, etc., were free from lesions. No apparent relationship between arthritis and taxonomic position, zoogeography, ecology, habits, diet, pathological panels and focal infection could be discovered. The varieties which had the most pronounced lesions were the anthropoid apes and baboons. Lesions were found not only in specimens exhibited in menageries but also in the material that was in its proper habitat when killed.

This monograph which is the result of painstaking observation and research is well worth study by roentgenologists and physicians and should be in the library of all those especially interested in the problem of arthritis, its etiology and pathology.

R. S. Bromer

Die Röntgentiefentherapie. Unter Mitarbeit von Fachgenossen zusammengestellt von Professor Hans Holfelder, O. Ö. Professor für allgemeine klinische Röntgenkunde an der Johann-Wolfgang-Goethe-Universität, Frankfurt A. M. Paper, price RM. 27; bound, price RM. 29. Pp. 341, with 264 illustrations. Leipzig: Georg Thieme, 1938.

This book, written partly by Holfelder and partly by several collaborators including Beutin, Englmann, Reisner, Töppner, Bulich, Engels, Teschendorf and others, is well printed on good paper and contains numerous and

effective illustrations. It constitutes an excellent description and discussion of the ideas and methods of Holfelder and his school. Therefore, it will be of interest to all radiologists who are interested in familiarizing themselves with these ideas and methods. In no way can it be regarded as a thorough discussion of all phases of radiotherapy, because a number of conditions have not been included at all or have only been mentioned incidentally. Especially interesting perhaps are Englmann's chapter on the microscopic changes following irradiation, and the chapter by Reisner and Holfelder on skin reaction and the rhythm of irradiation, as well as Teschendorf's chapter on roentgen irradiation and its effect on offspring.

A. U. Desjardins

A Historical Chronology of Tuberculosis. By Richard M. Burke, M.D., State Veterans Hospital, Sulphur, Oklahoma. Cloth. Price, $1.50. Pp. 84. Springfield, Illinois: Charles C Thomas, 1938.

This small book follows the subject of tuberculous infection from 5000 B.C. to the present.

If one is interested in knowing who did what and in what year then the purpose of the volume has evidently been fulfilled. It seems to the reviewer that any chronology should at the same time be supplemented with a bibliography of the events recorded; otherwise, the effort becomes a mere maze of dates which, without adequate knowledge of the significance of such dates, leaves the reader little improved. A chronology of any disease with an adequate accompanying bibliography would be of great value.

The authors have divided the book into an Ancient Period (5000 B.C.–1600 A.D.); a Premodern Period (1600–1800); and a Modern Period (1800——).

It would appear to the reviewer that nothing of significance happened in the year 1800 to herald it as the natal day of the modern era. Aside from the then and now little realized value of Laennec's contributions, little of real worth in our knowledge of tuberculous infection happened until 1882. It then took twenty-two more years to find a suitable method of therapy, and it appears to the reviewer that not until the nineteen twenties did the modern period truly begin. It was during these years that our knowledge of the pathology, chemistry, and therapy of tuberculosis really advanced. The latter portion of the book lags markedly in its recording of the great advances made in case findings and collapse therapy, and these must be considered as some of the foremost steps in any chronological record of tuberculosis.

It seems to the reviewer that such a compilation of dates without an accompanying bibliography is of interest only to the occasional reader and that it can serve no real purpose in the advancement of our knowledge of tuberculosis in the manner in which it should be advanced.

William M. Tuttle

The Physiology of Exercise: A Text-Book for Students of Physical Education. By James Huff McCurdy, A.M., M.D., M.P.E., Director of Physical Education, Springfield College, Springfield, Mass., etc., and Leonard A. Larson, B.A., B.P.E., M.Ed., Ph.D., Professor of Health and Physical Education, Springfield College, Springfield, Mass. Third edition, thoroughly revised. Cloth. Price, $3.75, Pp. 349. Philadelphia: Lea & Febiger, 1939.

This is the third edition of the present book; the dates of the first two editions are not given. Two new sections have been added: (1) a chapter on exercise for persons over forty years of age, and (2) a section on exercise for women. The authors deal interestingly with the purposes of physical exercise in the various age groups, reviewing the physiological and chemical aspects as well as the general effects of physical effort. In considering the effects of exercise upon the heart it is stated that the hearts of successful marathon runners as larger than average and that enlargement occurs immediately following a marathon race. Differing with this observation are the studies of Levine and others. They found that the hearts of the majority of marathon runners were remarkably normal as to size, and immediately following a race the hearts were actually smaller and remained so for approximately two hours before returning to their previous size. The book is interesting and practitioners should find in it considerable material of great value, particularly for the guidance of young persons and those above the age of forty.

Burgess Gordon

The Life of Chevalier Jackson: An Autobiography. Cloth. Price, $3.50. Pp. 229, with many plates. New York: The Macmillan Company, 1938.

This is indeed a most interesting account of

a most interesting and useful life. The book deals with the entire remembering years of the author. It traces admirably the early years of his practice, of the gradual interest and development of endoscopy. It relates the rise of a new type of medical endeavor in this country.

Certainly no man has done more to bring forth a new science within the science of general medicine. The story of this long course is told in the book. Such advances are not made in the short period of a year but through many years, and it seems to the reviewer that this is the real message that the book has to bear. It should give courage to those entering new fields and bring them to realize that there is much to do and that it can be done even though the beginnings are humble.

In parts, the book may give the impression that the author has dealt too fully with personal feelings and reactions, especially with those opinions which were fostered in the early years of life. It is the prerogative of all, however, to have such memories, and the relating of them the special prerogative of those who by their life work have attained a niche among the great in any field.

The work is well done and an inspiration, and the life portrayed a goal to those who view fine endeavor as something removed from the field of medicine. It again reveals that a science within a science can still be created.

William M. Tuttle

BOOKS RECEIVED

Principles of Roentgenological Interpretation. By L. R. Sante, M.D., Professor of Radiology, St. Louis University School of Medicine; Radiologist to St. Louis City Hospital and St. Mary's Hospital, St. Louis. Third Revised Edition. Cloth. Pp. 340, with 333 illustrations. Ann Arbor, Michigan: Edwards Brothers, Inc., 1940.

Radiodiagnostico. Tomo I. Fisica de los rayos X aparatos. By Gonzalo Esguerra Gomez, Profesor en la Facultad de Medicina de la Universidad Nacional. Cloth. Pp. 115, with 80 illustrations. Bogota, Colombia, S. A., 1938.

Radiodiagnostico. Tomo II. Sistema oseo. By Gonzalo Esguerra Gomez, Profesor en la Facultad de Medicina de la Universidad Nacional. Cloth. Pp. 335, with 400 illustrations. Bogota, Colombia, S. A., 1939.

La Roentgenchimografia Cardio-vascolare. By Prof. Pietro Perona, Incaricato di Radiologia nella R. Universita di Padova. Paper. Pp. 356, with 169 illustrations. Belluno: Casa Editrice Libraria A. Salvador, 1939.

Hepatolienographie mit Jodsol. Von Dr. Franz Beckermann, Sedkundärarzt der I. medizinischen Klinik der Hansischen Universität. Cardboard. Price, RM. 8. Pp. 88, with 65 illustrations. Leipzig: Georg Thieme, 1940.

Das Brustbein und seine Gelenke: Normale und krankhafte Befunde, dargestellt zum teil Mittels neuer röntgenologischer Methoden. (*Fortschr. a. d. Geb. d. Röntgenstrahlen*, Ergänzungsband 58.) Von Dr. E. A. Zimmer, Assistent am Röntgeninstitut der Universität Basel. Paper, price RM. 13; bound, RM 15. Pp. 70, with 81 illustrations. Leipzig: Georg Thieme, 1939.

Cancer Handbook of the Tumor Clinic, Stanford University School of Medicine. Edited by Eric Liljencrantz, M.D., Chief of Tumor Clinic, Stanford University School of Medicine, Consultant in Neoplastic Disease, United States Naval Hospital, Mare Island, and United States Marine Hospital, San Francisco. Cloth. Price, $3.00. Pp. 114, with 50 illustrations. California: Stanford University Press, Stanford University, 1939.

Medical Uses of Radium. Summary of Reports from Research Centres for 1937. Paper. Price, 35 cents. Pp. 48, with 5 illustrations. Medical Research Council, Special Report Series, No. 232. London: His Majesty's Stationery Office, 1938. (May be obtained from British Library of Information, 50 Rockefeller Plaza, New York.)

Medical Uses of Radium. Summary of Reports from Research Centres for 1938. Paper. Price, 30 cents. Pp. 49, with 5 illustrations. Medical Research Council, Special Report Series, No. 236. London: His Majesty's Stationery Office, 1939. (May be obtained from British Library of Information, 50 Rockefeller Plaza, New York.)

Wide Field X-Ray Treatment: The Value of the X-Ray Bath Method in Disease and Health. By S. Gilbert Scott, M.R.C.S.,

L.R.C.P., F.F.R., D.M.R.&E. (Camb.), Consulting Radiologist to the London Hospital; Honorary Radiologist to the British Red Cross Rheumatism Clinic, London: Honorary Physician Radiologist to the Charterhouse Rheumatism Clinic. Cloth. Price, 8/6. Pp. 80, with 13 illustrations. London: George Newnes Limited, 1939.

Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix. Third Volume. Statements of Results Obtained in 1932 and Previous Years (collated in 1938). Edited by J. Heyman, M.D., Stockholm. Paper. Pp. 149, with numerous tables. League of Nations Health Organisation. Official No. C.H. 1427. Geneva, 1939.

A Textbook of Surgery. By John Homans, M.D., Clinical Professor of Surgery. Compiled from lectures and other writings of members of the Surgical Department of the Harvard Medical School. Fifth edition. Cloth. Price, $8.00. Pp. 1272, with 530 illustrations. Springfield, Illinois: Charles C Thomas, 1940.

Reports on Medical Progress, 1939, as Published in the *New England Journal of Medicine*. Compiled and Edited by Robert N. Nye, M.D. Cloth. Price, $5.00. Pp. 562. Boston: Little, Brown and Co., 1940.

Die biologische Reaktion: Eine funktionelle Analyse und Synthese biometrischer Werte zur zahlemässigen Erfassung von: Allergie; allgemeiner Resistenz; spezifischer Resistenz; Krankheitsintensität; extensität aktiver Herde; Imunität. Von Dr. O. H. Bucher, Leiter des Schweiz. Antituberkulose-Institutes und der Klinik Satis in Seon, und Dr. C. C. Hofflin, Victoria, B. C. Cloth. Price, fr. 42.80 or RM. 25.70. Pp. 263, with 333 illustrations. Bern: Hans Huber, 1939.

The Medical Career, and Other Papers. By Harvey Cushing. Cloth. Price, $2.50. Pp. 302. Boston: Little, Brown and Co., 1940.

Symposium on the Synapse. By Herbert S. Gasser, Joseph Erlanger, Detlev W. Bronk, Rafael Lorente de Nó, Alexander Forbes. Cloth. Pp. 361–474. Springfield, Illinois: Charles C Thomas, 1939.

Vol. 43, No. 4

DEPARTMENT OF TECHNIQUE

Department Editor: Robert B. Taft, M.D., B.S., M.A., 105 Rutledge Ave. Charleston, S. C.

A NEW FILM ENVELOPE WITH ACCESSORY TRANSPARENT ENCLOSURE FOR ROENTGENOLOGIC REPORTS*

By WALTER W. FRAY, M.D., M.S., *and* LA VERNE L. NOLAN
ROCHESTER, NEW YORK

THE filing of roentgen-ray films and records has long been a problem to roentgenologists, particularly to those in hospital practice where space requirements prevent indefinite storage of films and records. The addition of new storage spaces, even if available within the hospital, does not furnish a solution, since their storage at more remote places necessitates increased labor cost.

The use of microfilm will furnish a transcript of the written or typewritten material, but it is doubtful if it represents an adequate solution to the permanent storage of roentgen-ray films. Our experience has shown that much of the finer detail is lost on any attempt at reproduction photographically of roentgenographic detail, particularly of fine lung or bone structure. It is possible that courts may finally accept such reproduced records of roentgenograms on the basis of decisions that the eye of the camera does not lie, but it should be remembered that compensations courts (in New York State) at the present time require the preservation of original films for five years. The manner in which an individual, either with or without intent to deceive, may modify his photographic technique to delete a fine fracture line of a bone or a fine linear fibrosis of the lung is appreciated by roentgenologists and photographers alike.

It becomes apparent that the original roentgenograms and particularly the original typewritten records of roentgen reports will be desired by the roentgenologist for review when the patient returns to the department for additional examinations. This will necessitate retention of original records over long periods, the length of time being dependent mainly upon the amount of space available and the legal requirements of the state or locality.

The immediate day by day problem of handling these records by different systems of filing has varied greatly in different departments of radiology. Many systems with which we are familiar require separate files for films, for index of names, and for requisitions and reports. Because of the multiplicity of files, a large storage space is required. Attempts have been many to reduce this filing space by combining files, but usually such attempts are at least partial failures, because the actual cubic content of the files is not greatly reduced. The simple transfer of the contents from one file and their subsequent storage of the envelopes and folders combined with reports in another file cannot aid, unless the second file not only is smaller but its contents remain unfolded. Folding has the further disadvantage that for its subsequent review time is lost in locating the proper report or record.

We have tried to solve the main problems attending filing of roentgen reports,

* From the Department of Medicine, Division of Radiology, University of Rochester, School of Medicine and Dentistry and the Strong Memorial Hospital, Rochester, New York.

requisitions, and films with the following ends in mind:

(1) To reduce the amount of filing space required to the absolute minimum.

(2) To permit the reviewing of old or previous roentgen-ray records of the patient with dispatch, saving the time of the roentgenologist during the routine period of the interpretation.

(3) To simplify the office procedure, thereby sparing the office personnel as much as possible of the labor burden.

(4) To effect economies in the overhead costs of routine work if possible, or at least to accomplish the above ends without increasing costs.

These ends we feel have been accomplished by devising a special double envelope—really a single envelope with accessory flat pocket—with a transparent window permitting the reading of the entire average roentgenologic record of the patient at a glance. The films are kept within the main envelope, while the typewritten reports appear in chronological sequence and can be read or reviewed without their removal. The secretary removes them only to add new reports. A carbon copy is preferably obtained at the time of the typing, the width of the paper conforming with the size of the history sheets of the main hospital record. The paper upon which the copy is made should be of heavy index stock to permit its easy insertion into the pocket. (The original is usually desired for the medical record.) If the original is pasted into the medical record (such pasting is undesirable, since it doubles the thickness of the record sheet and triples it if pasting is employed on both sides, and in addition, throws the sheet into undulatory folds and wrinkles which greatly increases the bulk of the medical record), the width of the glued sheet should be standard in width to utilize the full width of the medical record sheet. If the films leave the division of radiology, the typewritten copy is removed from the pocket and is left in the file in proper numerical sequence to indicate the removal of the films. No additional work is required except to make a notation on this record indicating date and the destination, or person to whom the films were sent. On return of the films a notation of their return is made, the typewritten copy is inserted back in the pocket, and the filing becomes complete with minimum effort. This method of handling loaned films is preferable to a separate small file of slips. This method, in our opinion, results in the commission of two errors:

(1) The slip is not made out in a busy department directly at the time of the loan due to the impact of other work, though the individual may have the best of intentions.

(2) The films are often returned during the evening or at other hours when the regular personnel is not present; hence the loan slips are not removed from the small file. Subsequent inquiry for these films will bring forth the misinformation that they have been loaned, and this has caused endless confusion with us, since the inquirer starts a fruitless tour of the hospital while the films are actually within the division of radiology, either stacked unfiled in the office or filed in the main file.

The commission of such errors is avoided with the system being described, since a visit to the main file will reveal either the entire envelope with the films, etc., or the typewritten reports with information in regard to the location of the films.

The routine in handling a request for examination proceeds as follows:

The intern fills out his request for examination, which to conserve space, utilizes the heading of the roentgenologic sheet for the medical record. On receipt of this sheet together with the appointment slip in the department of radiology the case is scheduled, after checking that it is a new case without previous examinations and that the name and unit number are correctly given.

Considering the patient a new one without previous record in the department, no index cards from the file need be typed—

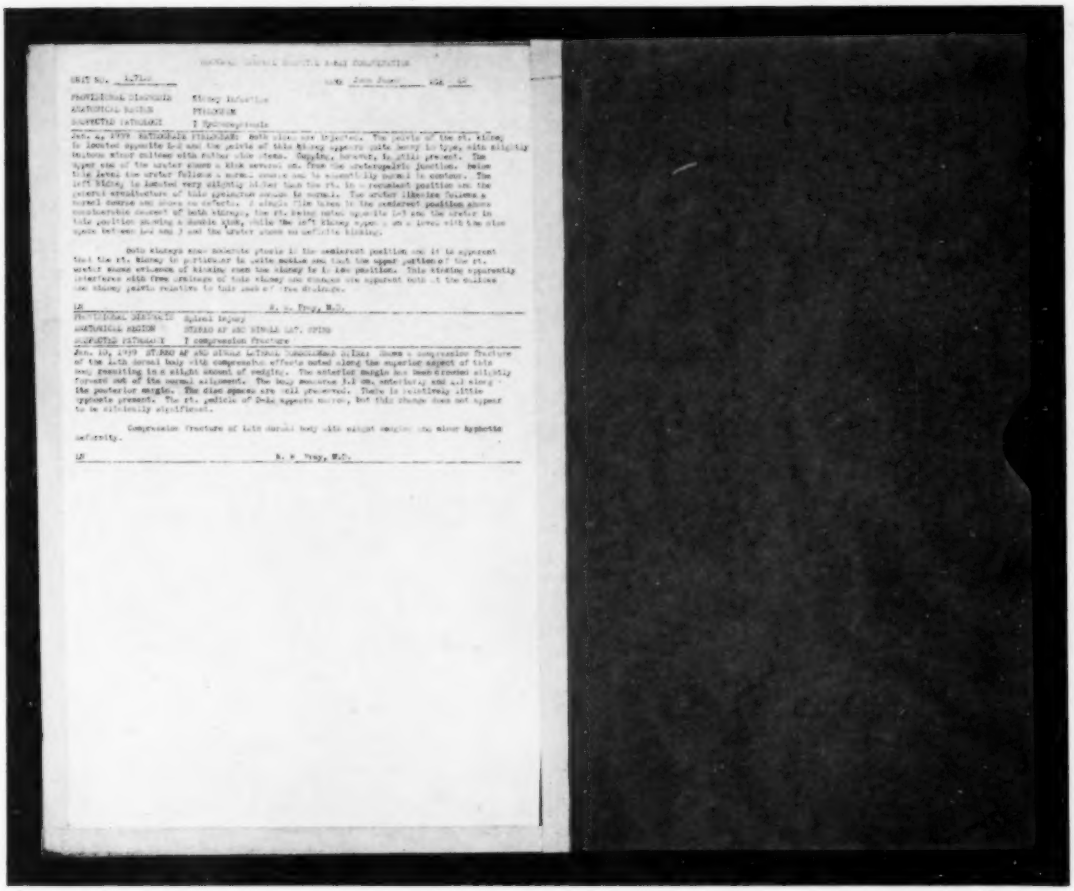

FIG. 1. Special envelope for 14 by 17 inch films showing enclosure for roentgenologic reports. The transparent front of cellophane (invisible in illustration) permits direct inspection of reports without their removal. These reports are typed in chronological sequence so that one may follow the progression of a lesion or disease without consulting and rearranging miscellaneous reports. The transparent enclosure shown in this illustration is on the left side of the envelope. By the manufacture of envelopes with either right or left enclosures, it is possible to arrange the file so that all even numbered cases have the enclosure on one side (left) and all odd numbered cases on the other (right). By this simple means, the number of film-numbers the eye must follow to find the desired one is reduced to one-half.

no additional hospital form need be filled out; the patient is simply scheduled for examination after the check shows that the case is a new one. Not even the envelope for the roentgenograms need be written upon. There is no need for name, unit, number, title of examination or date. When the films have been secured and dried, these are placed with a new folder, and the roentgenologic sheet for the medical record is slipped into the transparent pocket, and since this record sheet has already been checked for correct name and number, no further work is required until the time for interpretation.

When the film is interpreted, the secretary types the roentgenologic report on the medical record sheet, securing a carbon copy on the heavy sheet of paper with which the envelope comes supplied. The headings on the two sheets are so arranged mechanically with the carbon paper that the name and unit number appears on the copy. The type of examination, date, and type of case (O.P.D., private, Ward A, etc.) are typed in the first available line, and the report immediately follows.

If the case is an old one (one who has had previous roentgenologic examinations), the routine is even easier. The envelope for

films and reports is examined (checking of spelling and unit number is not required for correctness). No typing or writing is necessary on the envelope proper at the time of the arrival of the patient. When the films are interpreted, the report follows immediately after the last interpretation, conserving all possible space. Not only is this system simple for the clerks and secretaries to handle but it is evident that the work of the roentgenologist is greatly facilitated. He has at hand, without any manipulating, all previous reports on the patient ready for his inspection at a glance, visible through the transparent window.

SUMMARY

Common methods now in use require individual requisitions, index card systems for name, sequence systems for numbers, stamping or writing of data on the envelope containing films, and separate individual reports on interpretations. Each of these employ repetitious use of the name, date, unit number, etc. Records in many cases will show that the name of the patient has been written or typewritten a dozen or more times in caring for the record of a single patient who has had a succession of examinations.

To conserve time, labor, and stationery, but particularly to consolidate data and permit easy inspection of reports as well as to effect economies in storage space, a new envelope has been devised which is simple to use, spares the personnel, prevents many of the errors continually arising within the department and decreases the possibilities of loss of film or record. The few cents increase in cost of the envelope is more than offset by the saving in labor cost and economies in making and maintaining the records. Costs of stationery (requisitions, gummed paper, envelopes, and folders) should be reduced. These savings should be of importance to the hospital administration. The roentgenologist will be interested not only in these savings but will profit greatly by the expedition and ease with which his work at interpretation will be facilitated.

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ROENTGENOLOGIC DEMONSTRATION OF BLADDER PATHOLOGY

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THE introduction of the roentgen ray as an aid in establishing diagnoses in diseases of the urogenital tract materially decreased the need for instrumental procedures. The use of intravenous urography and cysto-urethrography has reduced manipulations to a minimum. To further eliminate as much as is possible prolonged instrumental studies, and to exclude these practices in debilitated patients, we have resorted to the following procedure:

First, the patient voids, emptying the bladder of as much of its urine content as possible. Under strict aseptic conditions, a No. 10 or No. 12 French soft rubber catheter is passed into the bladder and an estimation of the residual urine is made. The bladder capacity is now determined by means of sterile saline and the bladder again emptied. Then a quantity of air equivalent to one-half of the bladder capacity is injected into the bladder and the catheter removed.

The patient is now given an intravenous injection of diodrast and roentgen exposures of the urinary tract are made in the usual manner. As the dye is secreted from the kidney and enters the bladder, visualization of infiltrative masses such as neoplasms or diverticula are readily demonstrated.

Figure 1 shows a large intravesical intrusion of the mid lobe of the prostate in a patient, aged seventy-four, who had an acute prostatitis due to repeated manipulations prior to his reporting to our service.

A diagnosis of marked intravesical prostatic hypertrophy was definitely established in this case. This figure is shown merely to illustrate the results obtained by this procedure. The kidneys, ureters and bladder are outlined with a clearer picture of the bladder infiltration.

We have been able to establish a definite diagnosis without instrumentation in many cases, through an effective cysto-aerogram obtained with little manipulation and no trauma. The roentgenograms obtained show greater contrast and clarify the bladder pathology. The vesical end of the ureters is better visualized.

FIG. 1.

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

Skeletal System

Worth, H. M.: Use of lipiodol in localisation of spinal tumours 618

Lob, A.: Pathological-anatomical basis for roentgen appearance in healing of vertebral injuries 619

Taylor, R. G.: Anomalies of lumbosacral articulations 619

McKeever, F. M.: Tuberculosis of the knee in infancy and childhood 620

Meyerding, H. W., and Pollock, G. A.: March fracture 620

McReynolds, I. S.: Osteolytic osteogenic sarcoma 621

Blood and Lymph System

Häussler, G.: Demonstration of cerebral vessels with ethyltriiodostearate 621

Hämmerli, F.: Arteriography of the extremities with ethyltriiodostearate 621

Veal, J. R.: Pathologic basis for swelling of the arm following radical amputation of the breast 621

General

Hellman, L. M., and Irving, F. C.: The x-ray diagnosis of erythroblastosis 622

ROENTGEN AND RADIUM THERAPY

Gilbert, R.: The development of radiation therapy of some generalized diseases during the last ten years 622

von Wieser, W.: Roentgen therapy of epilepsy 623

Sgalitzer, M.: Experiences with roentgen treatment of epilepsy 624

Hess, P.: Roentgen treatment of chronic tonsillitis 624

Baensch, W.: Radium treatment of hemangioma 625

Patzold, E.: The evaluation of the blood findings in the roentgen therapy of blood diseases 626

Carrie, C.: Treatment of roentgen-ray leukopenia 627

Lüsebrink, H.: Changes in the white blood picture following treatment of lupus with grenz rays 628

ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

SKELETAL SYSTEM

Worth, H. M. The use of lipiodol in the localisation of spinal tumours. *Brit. J. Radiol.*, April, 1938, *11*, 211–226.

The general gross anatomy of the spinal cord and coverings is reviewed. The principal methods of injection are via the cisterna magna or by the lumbar route. Certain advantages and disadvantages claimed for both methods are summarized. Certain neurologists claim that the injection of lipiodol into the spinal canal is dangerous and harmful. The author has not been able to find any records of a fatal result. Elsberg found recent adhesions at operation after lipiodol injection.

Doses up to 5 cc. are necessary in order to recognize small changes. If a lumbar puncture with removal of fluid has been carried out very recently a relatively dry subarachnoid space prevents the free movement of the lipidol. The patient is placed and fixed in the supine position, and the lipiodol is studied on the fluorescent screen. The mass must be kept intact if possible. In the event of any suspicious appearance roentgenograms are taken at once. In many people there is a tendency for the lipiodol to become arrested at the site of the vertebral curves. In variations from the normal the lipiodol may become completely blocked, partially blocked, divided into two streams, or the mass may present a defect at its side, sides, or in its center. In cases of intramedullary tumors there is a tendency for the lipiodol to be dis-

placed to the sides of the canal, forming two columns. However, intramedullary expansion of the cord may not produce a block of this type. Extramedullary intradural tumors which produce obstruction may reveal "cup-shape" indentation in the border of the arrested lipiodol. However, an extramedullary tumor may produce a block without the characteristic appearance. Small globules may be separated from the mass. This may not be of pathological significance but the arrest of a number of globules has been reported in arachnoiditis.

This article has a number of very good illustrations.—*S. G. Henderson.*

Lob, A. Das Röntgenbild und seine pathologisch-anatomischen Unterlagen bei der Ausheilung von Wirbelsäulenverletzungen. (The pathological-anatomical basis for the roentgen appearance in the healing of vertebral injuries.) *Fortschr. a. d. Geb. d. Röntgenstrahlen*, Sept., 1939, 60, 199–213.

While much is known about the healing of fractures of the long bones, there are many unsolved problems relating to fractures of the vertebrae. Vertebral fractures have been much more common because of heightened activity in industry, transportation, and sport, particularly skiing. The differences of opinion which exist concerning the treatment of such fractures further indicates the necessity for a better understanding of the healing process. The author, on the basis of pathological specimens, recognizes two types of injury: (1) the simple vertebral body fracture with no involvement of the arch, the processes, or the discs; (2) vertebral body fractures complicated by injuries of these other structures.

Simple fractures lead to the familiar wedge-shaped vertebra with a zone of disordered spongiosal bone usually parallel to the upper or lower border. There may be some angulation of the anterior border with folding of the anterior longitudinal ligament. After the injury the osteoclasts remove the disordered bone and simultaneously an osteogenic cell layer forms and leads to endosteal callus in the course of a number of months. Very little callus forms subperiosteally and often no change is demonstrable at the margins of the vertebra.

The complicated fracture shows involvement of the superior or inferior plates of the body and there may be avulsion of a fragment from one of the anterior angles as viewed in the lateral plane. In injuries of this type the intervertebral disc is always involved and tears may extend into the nucleus pulposus. Associated fractures almost always occur in the pedicles and the fracture line usually runs obliquely. It is recognized much more commonly in the pathological-anatomical preparation than in the roentgen films and may be accompanied by injury to the spinous processes. If the fracture occurs near the articular surface of the pedicle, healing may result in solid bone ankylosis at the involved joint. The fragments avulsed from the vertebral body unite with very little callus formation and over a long period the contour becomes smooth and rounded. Portions of the intervertebral disc which penetrate the fracture site become fibrous, but rarely ossify. If the annulus fibrosus is injured, spicule, beak and lipping formations occur at the margins of the vertebral bodies as the result of enchondral ossification in a cartilaginous overgrowth. This occurs in the course of two to three months after the injury and may result in laminated new bone with normal bone marrow. Injuries of this type are almost always accompanied by tears of the supra- and interspinal and interarcuate ligaments. The anterior and posterior longitudinal ligaments generally withstand the injury. In the dorsal spine the ligaments about the costovertebral joints may also be torn and there is usually hemorrhagic infiltration of the surrounding soft tissues over a large area.

The overgrowth which occurs at the margins of the vertebral bodies following trauma is an expression of injury to the intervertebral disc just as it is in primary spondylosis deformans. Such formations do not occur at the site of a vertebral injury unless there has been an accompanying injury to the disc. They cannot properly be regarded as "periosteal callus." True callus is sometimes recognizable; it is limited in extent and duration and occurs at the fracture site.

In estimating the healing of vertebral body fractures, one must remember that the fracture is only a part of the injury and that great consideration must also be given to the ligamentous injuries which occur about the joints.—*W. A. Evans, Jr.*

Taylor, Raymond G. Anomalies of the lumbosacral articulations. *J. Am. M. Ass.*, Aug. 5, 1939, *113*, 463–465.

The fifth lumbar vertebra shows more anomalies than any other vertebra in the body. The commonest ones have to do with the

transverse processes and the articulations. The transverse processes may be short, almost rudimentary, long and slender, or broad and massive. The transverse process and the whole lateral mass may articulate with or may be actually fused with the sacrum. The articular facets are normally crescentic and the superior pair is slightly hollowed out and cuplike, the surface of the inferior facets being slightly convex to fit into the concavity of the facets of the vertebra below; normally they face laterally and slightly obliquely. The superior pair of joints of the fifth are generally of this type, but the inferior pair that articulate with the sacrum show wide variation in the direction the joint faces. Two main variations are relatively frequent. Each pair may face directly anteroposteriorly. A second variation shows the joint faces resting directly one above the other, facing in a caudad-cephalad direction. There may be a combination of any of these three types of joints. If one does not see through these joints in the routine type of anteroposterior roentgenogram they are abnormal as to their facing and the wider the articular process shows in the roentgenogram the more nearly the joints face anteroposteriorly. To see through these joints and to learn something of their condition, lateral and oblique views must be made.

Abnormal motion in these joints may result in damage to the joint or ligaments. With relaxed muscles and sudden unexpected strain, enough movement is possible either to damage the synovia or to strain the ligaments. Repeated damage to the same structure may sooner or later produce fibrous changes, scar tissue and in many instances calcium deposit in the injured tissues.

A consideration of extracts from some of the articles in the American literature shows that anomalies of the joints are common, that they give improper support to the body structures and are deficient in their weight-bearing and strain-resisting properties, and that the defects or anomalies allow damage to the joints and to their soft tissue supports, thereby being a fairly common and important cause of pain. It is obvious that most persons who have backs showing these anomalies are rather unsuited to hard manual labor as lifting and straining. They are more liable to injury than others with normal articular facets. Roentgenologic reports should call attention to these conditions.—*S. G. Henderson.*

McKeever, Francis M. Tuberculosis of the knee in infancy and childhood. *J. Am. M. Ass.*, Sept. 30, 1939, *113*, 1293–1299.

Author's Summary. For forty-seven patients in the first ten years of life suffering from proved tuberculosis of the knee joint, the most frequent age of onset was found to be within the first four years.

Fifteen patients, or 31.9 per cent, presented a bone abscess in the metaphysial or epiphysial region of the tibia or the femur early in the disease.

One patient remained well, with a normal knee joint, for eight years after extra-articular excochleation of an osseous focus. In five other patients this procedure failed.

Conservative treatment, or surgical procedures short of economical resection, accomplished no satisfactory results in the remaining forty-six patients.

Economical resection healed the tuberculosis in thirty-two of thirty-four patients, or 94.1 per cent, whom it was possible to follow for from one and a half to thirteen years.

The knee joint of a child ankyloses very readily after resection, and the percentage of successful fusions resulting from a single operation is as high as that for ankylosing operations on any other joint.

Extreme shortening after economical resection in infancy and childhood is not the rule; any marked degree occurred in only 30 per cent of the patients. In these it usually resulted from causes extraneous to the resection.

Severe aberrations of directional growth were associated in most instances with previous damage to the epiphyses. They occurred in only $33\frac{1}{3}$ per cent of the patients. Moreover, in these they were readily correctable by osteotomy.

From the evidence it seems reasonable to conclude that economical resection of the knee is not contraindicated prior to epiphysial closure, and this procedure should not be withheld until the age of 15 from children suffering from tuberculosis of the knee joint.—*S. G. Henderson.*

Meyerding, Henry W., and Pollock, George A. March fracture. *Surg., Gynec. & Obst.*, August, 1938, *67*, 234–242.

The authors discuss the various clinical features of so-called "march fracture," with special emphasis upon the predisposing and

exciting factors and the differential diagnosis. The roentgen evidence may be absent even though the diagnosis is strongly suggested clinically. The hair line fracture in the metatarsal bones may be visible only after repeated search. Later the fracture line may become easily visible after the subperiosteal new bone proliferation has supervened. Ten representative cases are reported. The condition may be confused with sarcoma and in all doubtful cases a biopsy should be done.—*P. C. Swenson.*

McReynolds, I. S. Osteolytic osteogenic sarcoma with a report of eight five-year survivals. *Surg., Gynec. & Obst.*, August, 1938, *67*, 163–168.

After discussing the gross and microscopic features of osteolytic osteogenic sarcoma as well as its tissue origin, the author reports on 8 five-year survivals. All were amputation cases and several had had one or more operative procedures to the tumor area prior to amputation. In a series of 131 cases studied from the Surgical and Pathological Laboratories of the Johns Hopkins Hospital, 47 per cent were in the second decade of life, 16 per cent in the third, and 8.5 per cent in the next three decades. Only 1 case was under the age of ten and 7 were over the age of sixty. Osteolytic sarcoma represented 24.1 per cent of all types of osteogenic sarcoma. Of 99 cases followed over a period of five years, 8 were alive; and 5 of the 8 lived approximately ten years or longer. Three died of metastases at six, seven and seven and a quarter years. In all, 92 per cent died from the effects of the disease prior to five years and 94 per cent died within eight years.

The author believes that osteolytic sarcoma may arise from benign giant cell tumor. The microscopic examination of these cases does not suggest that they are any less malignant but the several local operative procedures done in these cases probably would. The author cites one interesting case of metastases occurring seven years after amputation. In another the patient developed metastases three years prior to death which occurred five years after amputation. The metastatic lesions were kept under control by deep roentgen therapy. This is an unusually good palliation and suggests to the author that roentgen therapy should be given a trial in cases of pulmonary metastases. No change in the management of the treatment is suggested.

Perhaps the most important observation made in this study was that five-year survivals are less likely the younger the patient and the shorter the duration of symptoms.—*P. C. Swenson.*

BLOOD AND LYMPH SYSTEM

Häussler, Georg. Über die Darstellung der Hirngefässe mit Äthyltrijodstearat. (The demonstration of the cerebral vessels with ethyltriiodostearate.) *Fortschr. a. d. Geb. d. Röntgenstrahlen*, August, 1939, *60*, 171–173.

The use of this finely dispersed colloidal substance in the demonstration of the liver and spleen has been recently reported by Beckermann. It is superior to thorotrast in not being radioactive and in being completely excreted by the body in a few days. Excellent results were obtained in visualizing the vessels of the brain upon injection of a 20 per cent solution and no evidence of damage was encountered.—*W. A. Evans, Jr.*

Hämmerli, Fortunat. Über die Extremitätenarteriographie mit Äthyltrijodstearat. (Arteriography of the extremities with ethyltriiodostearate.) *Fortschr. a. d. Geb. d. Röntgenstrahlen*, August, 1939, *60*, 173–175.

Arterial injection of this substance is painless, but produces a sensation of increased heat in the extremity, and a rise of 2° C. may be detected in the extremity for two days.

For arteriography it is recommended that the exposed artery be injected under local anesthesia with 8–14 cc. of the warm 20 per cent iodine containing sol.—*W. A. Evans, Jr.*

Veal, James Ross. The pathologic basis for swelling of the arm following radical amputation of the breast. *Surg., Gynec. & Obst.*, Dec., 1938, *67*, 752–760.

Venographic studies and local venous pressure determinations can be used in ascertaining the rôle of venous obstruction as a causative factor in the production of edema following radical amputation of the breast. The author describes three types of postoperative edema: (1) The lymphatic edema, least common (10 per cent) of cases, due to blockage of both the superficial and the deep lymphatics usually by early postoperative infection or a recurrent lymphangitis or cellulitis of the arm and shoulder, but less often due to direct extension of carcinoma into the skin and subcutaneous tissues of the arm. The venogram shows no ob-

struction. (2) Edema due to venous obstruction of the soft pitting variety as contrasted to the brawny lymphatic type (most common—90 per cent of cases) caused by the pressure of the continuously spreading new growth or by its constricting action. New growth may invade the lumen directly and plug it by tumor mass or by secondary thrombosis. Scarring may also be a factor. Venographic studies show the occlusion of the axillary vein and demonstrate the development of new venous channels. Venous pressure determinations are of value if the obstruction cannot be visualized because it lies proximal to the entrance of the external jugular into the subclavian vein. Pressures are recorded from 19.5 to 140 mm. of water in the edematous arm. (3) Edema from lymphaticovenous obstruction, an advanced form of the second type leading into a combination of the first two. Infection is prone to occur in this type which further increases the lymph stasis. —*P. C. Swenson.*

GENERAL

Hellman, Louis M., and Irving, Frederick C. The x-ray diagnosis of erythroblastosis. *Surg., Gynec. & Obst.*, Sept., 1938, *67*, 296–298.

The authors present 3 cases of erythroblastosis of the hydrops variety in which the diagnosis was established (by means of the roentgen ray) prior to the birth of the infant. Because this type of erythroblastosis is incompatible with life, and because there is a 30 per cent familial incidence of the disease with 50 to 80 per cent chance of recurrence in the same family, the prenatal diagnosis is of more than academic interest. The diagnosis depends on the presence of an advanced edema of the soft parts which the authors say can be recognized in the roentgenogram as a thickening and increase in density of the soft parts, particularly striking in the scalp. This edema is not necessarily limited to this disease, however, so that the roentgen findings are not specific. It is unfortunate that the reproductions of the authors' roentgenograms are not very convincing.—*P. C. Swenson.*

ROENTGEN AND RADIUM THERAPY

Gilbert, René. Die Entwicklung der Strahlentherapie einiger generalisierter. Erkrankungen im Laufe der letzten 10 Jahre. (The development of radiation therapy of some generalized diseases during the last ten years.) *Strahlentherapie*, 1938, *63*, 385–392.

In this work the author considers radiation therapy in chronic leukemia, essential erythremia and in lymphogranuloma. Up to 1927, with the exception of animal experiments only so-called local segment irradiations of the human body were carried out. This type of procedure was classical irrespective of whether one had to deal with a local or a generalized affection. It has been known for a long time that leukemia and lymphogranulomatosis are radiosensitive. With the improvement of technique these two diseases began to be treated more successfully by the roentgen ray. At this time an attempt was made to irradiate the entire body. It was found that under this method of treatment in combination with arsenic medication, it was possible to prevent the appearance of a growing resistance to roentgen radiation. This statement was at first made by Naegeli and was later confirmed by Schinz and others. Naegeli is of the opinion that at first the individual suffering from leukemia should be treated intensively by oral and parenteral arsenic therapy. The results of the treatment must be judged by the condition of the blood picture as a whole and not by the number of leukocytes only. This form of roentgen treatment of leukemia is preferable to the old classical form, since the clinical results obtained by it are considerably superior and since to a certain extent the possibility of development of resistance to the roentgen ray is eliminated. Using this method of treatment good results were supposedly obtained by Cottenot and Sluys in cases of lymphatic leukemia.

In cases of erythremia or Vaquez's disease, Sgalitzer reported in 1937 to have obtained favorable results in 42 of the 44 cases treated by him roentgenologically. The results are very encouraging but just as in leukemia no cure is obtained. Using the generalized roentgen method of treatment, it is possible to lower the red cell count to 4,000,000 at a time when the white cell count does not decrease below 3,000.

In lymphogranulomatosis or Hodgkin's disease, the effect of the generalized roentgen treatment is different than in the other two diseases mentioned. Here it leads to severe general symptoms and consequently some authors prefer here roentgen treatment of the entire trunk of the body with large individual fields combined with local irradiations of the

tumor. This author uses four to seven ventral fields and a similar number of dorsal fields, all the fields overlapping. Under this arrangement the patient is given daily or every other day about 250 r until a total dose of about 1,000 r per field has been given.

On the basis of the results hitherto obtained it may be stated that the clinical results obtained from the general roentgen treatment of the body in cases of leukemia, erythremia and lymphogranulomatosis are quite contradictory and vary in the different diseases. Up to now the best results were obtained from this treatment in cases of leukemia and especially in cases of erythremia. The author is of the opinion that the data available are insufficient to permit discarding the old classical method; nevertheless it cannot be denied that this method of treatment is frequently effective in cases where the segmental method of treatment is ineffective.—*A. S. Schwartzman.*

Von Wieser, W. Röntgentherapie der Epilepsie. (Roentgen therapy of epilepsy.) *Strahlentherapie*, 1938, *62*, 649–666.

In 1917 Kodon was the first to report favorable results obtained from the treatment of epileptics by means of roentgen irradiation of the skull. In 1913 Strauss treated a similar case in a similar manner but reported it only in 1919. Up to the present, twenty-two different authors have employed roentgen therapy in the treatment of epilepsy. Of all these authors, only four came to the conclusion that this mode of treatment should not be used, while the remainder have recommended this mode of treatment. A study of the 185 hitherto published cases reveals that in 51 of them (28 per cent), the condition remained unchanged, in 73 (39 per cent), the condition was improved and in 61 (33 per cent), the condition was very much improved or cured. Results of this type must be considered very satisfactory since they cannot be reproduced by any other known method of treatment.

The author believes that the reason this method of treatment of epilepsy did not achieve a greater popularity in the last twenty years may be explained by the following considerations: The deeply rooted belief of the incurability of epilepsy; the lack of clearness regarding the etiology and pathology of this disease which exists even today; the well known fact that especially in epilepsy spontaneous remissions which may last for years may occur; the lack of clarity regarding the results hitherto obtained; the apparent lack of permanent results; the difficulty encountered in an attempt to carry out the roentgen treatment and the presumable danger of roentgen therapy in general and its danger in epilepsy in particular. The main answer to all these objections is factual, namely, of the 185 published cases only 28 per cent failed to respond to treatment while 72 per cent were favorably influenced and in 33 per cent of these apparently a cure was obtained. The objection that spontaneous remissions occur in epilepsy is not applicable to these figures since the percentage of cures is too large to be explained by such accidental remissions. Even though the material available is not large enough to permit absolute conclusions, nevertheless it is sufficiently large to show that this method of treatment is quite promising. The fact that in some of these cases the improvement or cure persisted up to the time this article was published, that is, over five years, is indicative that there is a definite justification for this type of treatment. The objections regarding the difficulty of carrying out this method of treatment have been practically eliminated during the last few years, namely, it has been found that following a strict individualization of each case and following the simplest rules, no difficulties are encountered. As to the objections of danger of this method of treatment it may be stated that hitherto no injurious effects have been reported. The author concludes his work with the recommendation that in each case where roentgen therapy of epilepsy is instituted, an attempt should be made to elicit as much as possible the presumed cause of the disease, the course of the disease, the exact nature of the attacks and their intensity and number, conditions which lead to the appearance of the attacks and the medication employed and its effect up to then. On the basis of these data, one is in a position to determine approximately the roentgen dose necessary and the time of exposure. In each case an attempt should be made to use the smallest possible dose at the beginning.

At present this author uses five skull fields, each of 6×8 cm. The fields are used one on the right and left of the lateral surface of the skull, one on the forehead, one on the vertex and one on the occiput. A sixth skull field may be

used directly over the medulla oblongata. In cases where the localization of the focus is approximately known the first field chosen should be situated at a considerable distance from the focus. During the following irradiations the field is chosen closer and closer to the focus. In cases where the localization of the focus is not known the first field used by the author is that situated in the region of the back of the neck. The intervals between the roentgen treatments should be relatively long in order to prevent cumulative effects.—*A. S. Schwartzman.*

Sgalitzer, Max. Erfahrungen mit der Röntgenbehandlung der Epilepsie. (Experiences with roentgen treatment of epilepsy.) *Strahlentherapie*, 1938, *62*, 667–679.

The basis for the roentgen treatment of epileptic diseases is the possibility of influencing disturbances of the water metabolism in the brain by the roentgen treatment, and of influencing inflammatory changes of the central nervous system; the inflammatory changes of the central nervous system may be influenced roentgenologically by way of the vascular system either through the vasomotors or through direct influence on the capillary endothelium; in cases of epilepsy due to glandular dysfunction the hypophysis may be influenced; finally the roentgen irradiation may also exert its effect as a vasodilation promoting agent. Of the 78 cases of epilepsy of varied etiology observed by the author in the course of two years, which showed no improvement whatsoever under direct treatment, one-third remained uninfluenced by roentgen irradiation. Of the remaining two-thirds more than three-fifths were favorably influenced to some extent while not quite two-fifths were very favorably influenced. The 78 cases treated could be classed into eight groups: (1) traumatic epilepsy; (2) epilepsy due to heredo-degenerative processes; (3) hydrocephalic forms of epilepsy; (4) epilepsy conditioned by brain tumors; (5) epilepsy due to inflammatory processes; (6) glandular dysfunction forms of epilepsy; (7) toxic forms, and (8) genuine epilepsy.

By far best results were obtained from the irradiation in those cases where the epilepsy was due to hydrocephalus or to some disturbances of the water metabolism of the brain. The roentgen doses necessary to obtain results in these cases are considerably larger than in other forms of epilepsy (with the exception of cases where the epilepsy is due to a tumor), but even here the dose is still below that which would lead to a loss of hair.

The dose of roentgen rays and the technique of irradiation should be adjusted to the individual case, to the age of the patient, to the reaction of the patient, etc. With the exception of the cases of epilepsy due to tumor, the hydrocephalic cases require the highest and the genuine and inflammatory cases the smallest doses of roentgen radiation. The first irradiation is given with very small doses in order to determine the mode of reaction of the patient. Four to five skull fields must be irradiated.—*A. S. Schwartzman.*

Hess, P. Die Röntgenbehandlung der chronischen Tonsillitis. (The roentgen treatment of chronic tonsillitis.) *Strahlentherapie*, 1938, *63*, 393–398.

The author is of the opinion, based on many years of experience, that the roentgen treatment of chronic recurring tonsillitis is a valuable and reliable therapeutic method when the indications are correct and when the treatment has been technically correctly performed. Hess treated a number of cases which could be classed as follows: (*a*) chronic recurrent angina without hyperplasia and without complications; (*b*) chronic recurrent angina with inflammatory swelling and regional swelling of the cervical lymph glands; (*c*) chronic recurring angina with hyperplasia and cleft formation.

In each of these cases the radiation technique, which no doubt is of significance in the the results obtained, was essentially the same and was as follows: 180 kv., 0.5 mm. Cu and 1 mm. Al filter, 30 cm. distance and field size of 6×8 cm.; the irradiation was carried out in two sittings, each tonsil with a dose of 165 r. The two irradiations were carried out on successive days. It is not desirable to irradiate both tonsils on the same day because following the irradiation there appears a slight swelling, which usually disappears after twenty-four hours. The same irradiation is repeated fourteen days later. Not in a single case were more than two irradiations carried out. Not in a single case were any complications observed which could have been referred to the irradiation.

Of the 124 cases treated in this manner, 101 could be followed up, and the results obtained were as follows:

Of the 101 cases, 30 of which belonged to

Group (*a*), 17 to Group (*b*) and 54 to Group (*c*), 64 were cured, 23 were improved and 14 remained uninfluenced. It appears from the above that best results were obtained in Group (*a*). In the group designated as improved, some patients developed recurrences and some had complications referring to the heart and joints which were not satisfactorily influenced.

Very satisfactory results were obtained in Group (*b*) so that it appears desirable to use roentgen irradiation as the method of choice in all cases of recurrent angina with involvement of the cervical lymph nodes. The good results obtained here are partly due to the extensive and more severe focus of inflammation. Less satisfactory are the conditions in Group (*c*). In these cases, in spite of the improvement, the hyperplasia persists but the improvement is manifested in the elimination of the angina and of the complications. In some of the cases of this group designated as improved, the complications referring to the heart, joints, and kidneys remained, but probably in a somewhat milder form.

On the basis of the results obtained, the author states that the chronic recurrent angina with participation of the regional lymph node is excellently influenced by roentgen irradiation. In the chronic recurrent angina without hyperplasia and without complications, good permanent results are obtainable. Only in 10 per cent of the cases is the treatment ineffective. In cases where the recurrent angina is combined with hyperplasia and crypt formation, the condition remains refractory to roentgen treatment in about 20 per cent of the cases. In these cases under the influence of roentgen treatment the attacks may fail to occur but the hyperplasia persists. This method of treatment may be recommended as very effective for cases of carriers of diphtheria bacilli. Roentgen irradiation and operation do not exclude each other but rather complement each other.—*A. S. Schwartzman.*

Baensch, W. Über die Radiumbehandlung der Hämangiome. (The radium treatment of hemangioma.) *Strahlentherapie*, 1938, *63*, 496–505.

It should be considered as axiomatic that the radium treatment of tumors of the vascular system is the method of choice. Apparently, however, this fact has as yet not been recognized among pediatricians and practitioners in general. In many instances methods of treatment are used which are unsuccessful; thus, for instance, carbon dioxide snow is frequently employed in the treatment of deeply extending cavernomas even though logically one could not expect a cure from this method of treatment. In many other instances surgical treatment is employed and in many instances gives unsatisfactory results especially in cases where suitable radium therapy would give ideal cosmetic results. In consideration of the above, the author believes he is justified in presenting some of his personal experiences with the radium treatment of hemangioma.

The use of radium therapy as well as the choice of technique must be based on a thorough knowledge of the structure of the different types of blood tumors. The technique of the radium application is based on the structure and position of the blood tumor. The first form of blood tumor is represented by the simple angioma or capillary plexiform angioma. In cases of this type there occurs an irregular budding of capillaries into the healthy tissue of the neighborhood. This process is especially clearly observed in early infancy. Histologically the epidermis remains unchanged. A single capillary network penetrates into the cutis on the periphery of which the vessels appear relatively small and increase in caliber centralward. Clinically, angiomas of this type are either transparent red or bluish, depending on the predominance of the arterial or venous system. The extension of this type of tumor through vascular budding occurs especially during the first months of life, at which time it is quite rapid. Hemangioma of this type, which at birth may be the size of a pea, may increase four to five times in size during the first two months of life. As a rule they do not extend beyond the level of the surrounding skin.

A basically more deeply penetrating form of blood tumor is the cavernous hemangioma. This presents in the subcutis sponge-like vascular dilatations of considerable size. In the microscopic picture one finds large blood sinuses. Also here the color depends on the predominance of the arterial or the venous components. Where the arterial components predominate considerably the tumor may actually pulsate. Tumors of this type have a predilection for the skull especially in the regions of the so-called embryonal clefts and therefore they have been designated as "fissural hemangiomas." They are found unusually frequently

on the inner angle of the lids, on the upper lip, as well as below the ear. A knowledge of these facts is essential since cavernomas of this type are not as a rule limited only to the visible and palpable surface but penetrate through the bony gaps into the deeper tissue and may extend intracranially. This is especially true for the cavernomas situated in the medial angle of the lids. A location of this type may in some instances lead to meningeal complications. Next in frequency tumors of this type are localized in the region of the shoulders as well as in the region of the vulva.

The two types of tumors mentioned above are of a benign character. A third type of tumor is malignant in nature and is known as angioplastic sarcoma. Histologically a picture of hemangio-endothelioma is obtained. Tumors of this type are found more frequently in the visceral organs than in the region of the external skin.

The treatment of the tumors described above should be instituted as early as possible. On the basis of a study of 230 cases Baensch is of the opinion that the optimal time for radium treatment is the period from four to five months of age; the general condition of the child, however, should be considered. The technique of radium treatment varies. The mildest form is the paste and wax mixture containing radium emanations used extensively especially in the United States. This type of operation is especially suitable for simple angioma. This paste because of its limited content of radium must be repeatedly applied and the method is therefore protracted and time consuming. The second method of treatment is the so-called moulage treatment in which the radium preparation in beeswax is fixed over the affected region. Also this method of treatment is applicable only to the superficially situated capillary angioma and this method of treatment is also protracted and time consuming requiring a number of applications. The third method of radium application is the radiopuncture, that is, the introduction of the radium into the tissue in the form of needles. The author employs for this purpose three types of needles containing 1 mg., 2 mg., and 4 mg. of platin-iridium filtered needles. When this method is employed the external skin remains completely intact while the vascular perforation is made to degenerate from below. On numerous experiments it was proved that one does not deal here with a mechanically conditioned subcutaneous scar shrinkage but that the results obtained are due chiefly to degeneration of the vessels as a result of the irradiation. On the basis of his own experience Baensch considers the radiopuncture of the blood vessels as the method of choice of treatment of hemangioma, especially of the cavernous type.—*A. S. Schwartzman.*

Patzold, E. Zur Bewertung der Blutbefunde in der Röntgentherapie der Blutkrankheiten. (The evaluation of the blood findings in the roentgen therapy of blood diseases.) *Strahlentherapie*, 1938, *62*, 710–713.

In chronic leukemic diseases roentgen therapy may lead in most cases to a restoration of the working ability and of the health for a given length of time. It is necessary to determine in each individual case of this type whether the type and stage of the disease offer any favorable prospect from the use of roentgen rays. The most important factors for this evaluation are a careful study of the general condition and a thorough blood examination.

A study of the literature shows that most authors recommend irradiation of cases of acute leukemia. No final answer can be given to the question whether in acute leukemia one deals with a septic process which affects the leukopoietic system in a severe manner or whether one deals with an acute form of the otherwise chronic disease. A further study of the literature reveals not a single case in which roentgen therapy led to a very favorable influence or to a cure. It may be assumed, therefore, that irradiation in this type of case decreases still further the protective measures of the body by injuring the mature white blood cells. On this basis, therefore, this author warns against roentgen treatment of acute cases of leukemia. The following view is assumed by the author regarding the roentgen therapy of chronic leukemia: In the first place the indication of roentgen treatment must be based to some extent on the degree of manifestation of the disease. In these cases the blood findings proper are of secondary significance. The number of white blood corpuscles alone must never be used as the basis for roentgen therapy. Even with a leukocyte count of over 100,000 the general condition may be quite satisfactory and there may be no necessity for roentgen irradiation. In each case of chronic leukemia

the indication for irradiation must be based on an evaluation of the entire blood picture. In cases where the blood picture is of a nature which indicates the desirability of roentgen irradiation, a pure qualitative blood picture as a whole must not serve as a contraindication to irradiation. The presence of a large number of immature cells is no contraindication to roentgen irradiation if one is not dealing with the terminal stage of the disease. Even an extremely poor function of the erythropoiesis is no contraindication to roentgen therapy since the poor erythropoiesis may be due chiefly to an injury of the blood forming organs by the leukocytic hyperplasia. In cases of this type roentgen therapy is actually followed by an increase of the red cell count, proving, therefore, the degree of effectiveness of the therapy. In cases, however, where roentgen therapy is followed by a further increase of the anemia, this response points to irreparable destruction of the erythropoietic tissue and further roentgen therapy is useless.

During irradiation an attempt must be made not to obtain a very rapid destruction of the leukocytes. Every second day a thorough study of the blood must be carried out during the irradiation. The irradiation technique must, therefore, also prevent a rapid destruction of the leukocytes. Considerable attention must be paid also to the behavior of the lymphocytes. A rapid decrease in the number of lymphocytes in association with a high leukocyte count is a dangerous sign and in each case where the lymphocyte count decreases to 2,000 the irradiation must be discontinued. In cases where irradiation is followed by a decrease in the number of red cells, by a decrease in the hemoglobin, and by an increase of the reticulocytes, irradiation must also be discontinued.

In chronic lymphadenoses attention may be called to two factors: The constant decrease of the thrombocytes is progressive with the progress of the disease. The hyperplastic lymphadenoid tissue in the glands and in the spleen requires large radiation doses which may be injurious to the radiosensitive cells of the myeloid series. A decrease of the absolute granulocytes up to 3,000 and a decrease of the thrombocytes to 100,000 necessitate a discontinuance of roentgen therapy in lymphatic leukemia.

Just as in the leukemic diseases, also many cases of lymphogranulomatosis may be favorably influenced by roentgen irradiation. Great care is necessary, however, in the choice of proper cases suitable for this treatment. In cases of acute lymphogranulomatosis combined with septic temperature, a leukopenia and a rapidly increasing anemia, radiation therapy is actually injurious. Of the other forms, especially the localized type is suitable for roentgen treatment. Also in lymphogranulomatosis, therefore, the radiation therapy must be carefully controlled and regulated by a thorough study of the blood.—*A. S. Schwartzman.*

Carrie, C. Zur Therapie der Röntgenstrahlenleukopenie (The treatment of roentgen-ray leukopenia.) *Strahlentherapie*, 1938, *63*, 183–187.

Feller recently reported, on the basis of experimental studies, that the effect of radium on the blood picture is similar to that of benzol, but that definite differences are present on the basis of which the two effects cannot be considered as fully identical. Friemann was able to confirm the occurrence of leukopenia following benzol intoxication in individuals employed in certain industries and later he was able to obtain experimentally the leukopenia in animals. Friemann later found that the experimentally produced benzol leukopenia in animals may be eliminated or prevented by the administration of vitamin C. In consideration of these findings an attempt was made by this author to determine the effect of vitamin C on roentgen-ray leukopenia.

It has been found that roentgen irradiation is followed by a definite decrease of the white cell count, especially when the irradiations have to be given at short intervals of time in the course of a long period, for instance, in cases of treatment of malignant tumors. The use of vitamin C by this author revealed that the roentgen leukopenia can be favorably influenced by it. It is conceivable that during the roentgen irradiation the normal vitamin C content is decreased and that the additional administration has a favorable effect on the leukopenia. Especially good results are obtained when the vitamin C administration is instituted at the same time as the roentgen treatment. It is desirable, therefore, to begin the vitamin C administration simultaneously with the roentgen irradiation. The impression was also obtained that roentgen irradiation was better tolerated by all the patients who received the vitamin C.—*A. S. Schwartzman.*

Lüsebrink, Hans. Veränderungen des weissen Blutbildes nach Grenzstrahlenbehandlung Lupuskranker. (Changes in the white blood picture following treatment of lupus with grenz rays.) *Strahlentherapie*, 1938, *63*, 77–81.

In the literature a number of changes in the white blood picture following treatment of the skin with grenz rays have been reported. In most of the cases these changes were observed a limited length of time following the irradiation. In some instances the blood picture was studied from a few minutes up to twelve to twenty-four hours following the irradiation. Leukocyte variations up to 2,000 per cu. mm. have been described. In studies of this type the physiologic daily rhythmic variations in the blood picture must be considered. Sabin and her coworkers have observed variations in the leukocyte count for which no demonstrable reason could be elicited, presumably occurring every fifteen minutes and of a considerable degree. In studying the effect of the grenz-ray irradiation one must, therefore, be extremely careful and must make absolutely sure that the variations are not physiologic but actually the result of the irradiation.

This author studied the blood picture of irradiated lupus patients at intervals of forty-eight hours and these studies were carried out in the course of four weeks. The blood was always obtained on an empty stomach at the same time of the day and under approximately the same environmental conditions. In about 50 per cent of the cases studied the lupus focus was superficial and was removed by means of an electric snare after which it was irradiated. In the remaining 50 per cent the lupus focus was irradiated only. The surface irradiated varied from 100 to 300 sq. cm. The dose employed was always 4,000 r. All the patients studied were on a salt poor diet.

At first the leukocyte count was obtained daily on 15 patients. In 14 cases the following day after the irradiation there was observed a decrease in the leukocyte count but this was not comparable with the decrease of the leukocyte number reported in the literature presumably observed under similar circumstances. In only one case could a decrease in the leukocyte count not be observed in the days following the irradiation. In 2 cases the leukocyte count was somewhat increased twenty-four hours after irradiation but during the following days it definitely decreased. The maximum leukocyte count obtained in these cases varied between ten and eleven thousand.

Besides the leukocyte count a differential count was also carried out. A definite variation could be observed only in the leukocytes and in the eosinophiles. No difference was found in the cases where the focus was previously removed and then irradiated and in the cases where irradiation alone was carried out.

In 13 of the 15 cases studied the number of the lymphocytes increased reaching the maximum in four to six days after which it returned to normal in a few days, and reaching another maximum fifteen to twenty days after the irradiation. The second maximum was not as pronounced as the first.

Two maxima were also found in the eosinophiles, the first appearing on the sixth to the eighth day and the second on the fifteenth to twentieth day after the irradiation.

In each case the blood sedimentation rate of the red cells was studied but apparently no demonstrable influence on the irradiation was observed.

Nothing definite can be stated as to the reason for this variation in the white blood cells. In all probability one is dealing here with an absorption of specific substances from the lupus foci conditioned by the influence of the rays; it is also conceivable that the vegetative nervous system may originate these variations. Further comparative studies on healthy and tuberculous skin may elicit the nature of these changes.—*A. S. Schwartzman.*